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Discovery of *N*-pyridoyl-Δ^2-pyrazolines as Hsp90 inhibitors

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Abstract

Hsp90, as a key molecular chaperone, plays an important role in modulating the activity of many cell signaling proteins and is an attractive target for anticancer therapeutics. Herein, we report the discovery of *N*-pyridoyl-Δ^2-pyrazoline analogs as novel Hsp90 inhibitors by integrated approaches of drug design, organic synthesis, cell biology, and qualitative proteomic analysis. Novel chemical compounds were designed and optimized in the adenosine triphosphate-binding site of Hsp90; lead optimized compounds were found to have significant interactions with Asp93 and other amino acids crucial for Hsp90 inhibition. The designed compounds were synthesized by a two-step procedure; different aromatic aldehydes were reacted with various acetophenones to form substituted 1,3-diphenyl-prop-2-enones (**Ic–Io**), which upon reaction with isonicotinic acid hydrazide in the presence of glacial acetic acid form *N*-pyridoyl-Δ^2-pyrazoline compounds (**PY1–PY13**). Compounds **PY3**, **PY2**, and **PY1** were identified as potential leads amongst the series, with promising anticancer activity against human breast cancer and melanoma cells, and the ability to inhibit Hsp90 similar to radicicol by drug-affinity responsive target stability proteomic analysis in a whole-cell assay.

KEYWORDS
anticancer activity, inhibitors, pyrazole, rational drug design

1 | INTRODUCTION

Hsp90 (heat shock protein 90) is a prevalent protein in mammalian cells. Hsp90 functions as a molecular chaperone in the conformational maturation, stability, and trafficking of several client proteins into their biologically active forms.[1] Many Hsp90 client proteins are over-expressed in cancer and are responsible for unrestricted cancer cell proliferation and survival.[2] Prominent oncoproteins that are stabilized and assisted by Hsp90 for oncogenesis are BRAF, Akt, Her2, cdk4, Src, Flt-3, hTert, c-Met, Bcr-Abl, and so forth.[3,4] Inhibition of Hsp90 results in the simultaneous destabilization and degradation of multiple oncogenic client proteins, leading to cancer cell growth inhibition and apoptosis.[5] The pharmacologic blockade of the Hsp90 function is claimed to have a combined inhibitory activity on all the hallmark traits of malignancy.[6] In addition, Hsp90 has been identified as an important extracellular mediator for tumor invasion,[7] and the expression of Hsp90 is also found to be amplified in cancer cells than normal cells.[8] Thus, the discovery of Hsp90 inhibitors is considered an important endeavor for anticancer drug development.

The complex natural product geldanamycin (GA) obtained from *Streptomyces hygroscopicus* was the first natural Hsp90 inhibitor reported.[9] Although too toxic to be developed as an anticancer drug,[10] its optimization by semisynthesis resulted in two promising derivatives: 17-allylamino-17-demethoxygeldanamycin (17-AAG) and 17-(2-dimethylamino)ethylamino-17-demethoxygeldanamycin (17-DMAG), which are more bioavailable than geldanamycin.[11,12] The concern regarding the toxicity of geldanamycin analogs due to their redox-active quinone moiety[12,13] led to the discovery of similar pharmacophoric compounds, such as macbecins[14] and herbimycins[15] with potent anticancer activity, which are presently under clinical trial. Radicicol (RAD), an antibiotic obtained from *Chaetomium chiversii*, is the

Abbreviations: DARTS, drug-affinity responsive target selectivity; Hsp90, heat shock protein 90; GA, geldanamycin; RAD, radicicol.

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most potent inhibitor of Hsp90 in vitro, but the reactivity of its epoxide group and the sensitivity of its conjugated double bonds to Michael additions render it inactive in vivo.[16] Gedunin, a tetranortriterpenoid isolated from the Indian neem tree (*Azadirachta indica*), which was reported to have anticancer, antimalarial, and anti-inflammatory properties, is under clinical investigation.[17,18]

Experience with natural products generated interest in alternative chemotypes. The purine class of compounds were the first synthetic compounds discovered to have potent Hsp90 inhibition.[19] Using high-throughput screening, a novel 3,4-diaryl pyrazole resorcinol (CCT018159) was identified to have potent Hsp90 inhibition.[20] NVP-AUY922 (VER52296) is an isoxazole derivative initially developed by optimization of a lead compound (CCT018159) and exhibits strong anticancer activity against many mammalian cancer cells.[21] Computational approaches have produced many types of small-molecule Hsp90 inhibitors, including pyrazoles,[22] resorcinol-containing triazoles,[23] isoindoles,[24] imidazoles,[25] indazol-4-ones,[26] and so forth. The focused approach on the discovery of Hsp90 inhibitors credited with many compounds in clinical trials such as NVP-AUY922 (phase II; Novartis),[27] ganetispib (STA-9090, phase II; Synta),[28] XL-888 (phase I; Exelixis),[29] PU-H71 (phase I; Memorial Sloan–Kettering Cancer Center),[30] PF-4929113/SNX-5422 (phase I; Pfizer),[31] and so forth (Figure 1). Though adenosine triphosphate (ATP)-binding site ligands are diverse in their chemical structure, they often bind to multiple proteins due to their nonspecificity. Nonselective ATP-binding ligands interact with many proteins, exhibiting toxicity and leading to the failure of a drug.[32,33] The N-terminal domain of Hsp90 is homologous to the members of the Hsp90 family, as well as to the members of the ATPase/kinase GHKL superfamily.[34] Molecular design and optimization of a selective N-terminal domain Hsp90 inhibitor is a challenging and complex process. Integrated approaches of bioinformatics, medicinal chemistry, and polypharmacology are to be given importance in developing Hsp90 inhibitors.

In continuation of our quest toward the discovery of small-molecule inhibitors of Hsp90,[35–38] in this article, we report the molecular modeling, chemical synthesis, and biological evaluation of *N*-pyridoyl-Δ^2-pyrazolines as Hsp90 inhibitors.

2 | RESULTS AND DISCUSSION

2.1 | Molecular modeling and docking simulations

We began our study by formulating a hypothesis to simulate constraints that approximate better interactions in the ATP-binding site of Hsp90. The initial approach treats this binding site as rigid

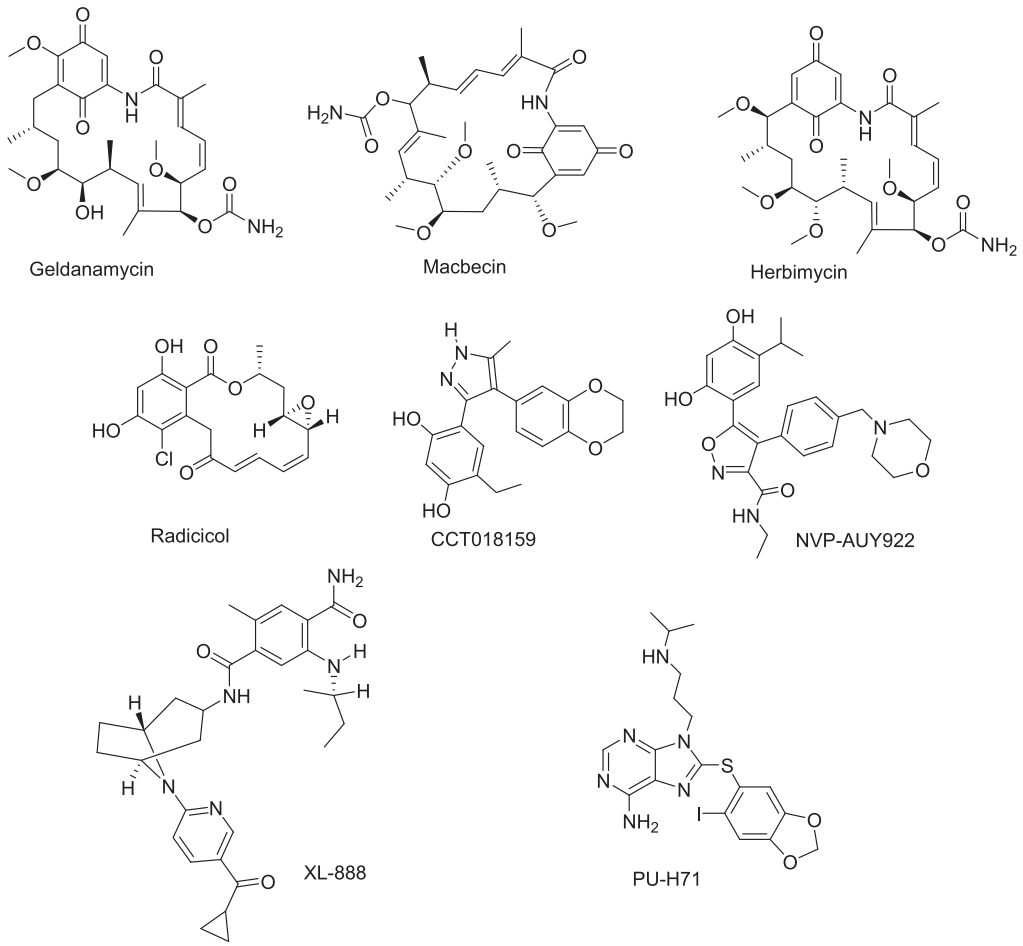


FIGURE 1 Representative example of potential Hsp90 inhibitors of both natural and synthetic origin

while probing the conformational freedom of test ligands to establish a complementary shape in the active site. Pyrazole scaffold inhibitors of Hsp90 and insights gathered from the study of the ATP-binding site of Hsp90 motivated the selection of a trisubstituted pyrazoline scaffold for targeting Hsp90 protein.[22,25,39,40] Active site prediction by DoGSiteScorer reveals the ATP-binding site as the best binding pocket for Hsp90 protein (Table S1).[42] The validation of docking methodology through the "pose selection" approach by superimposing the crystal ligand and the redocked ligand of Hsp90 protein shows similar binding interactions, binding alignments, and satisfactory RMSD between superimposed crystal ligand and redocked ligand (Table S2).[42] Schrodinger's Glide XP docking[43] of pyrazoline analogs in the rigid binding site of Hsp90 (PDB ID: 1YET)[44] endorse PY series having significant binding interactions with Hsp90 protein (Figure 2a–d). The detailed docking interactions are given in Table S3. The structure–activity relationship of the lead molecules of **PY** series was explored considering the binding interactions and their orientations in the ATP-binding site of Hsp90, with natural Hsp90 inhibitor GA and synthetic heterocyclic ligand "NVP-AUY922" (Luminespib) protein complexes. The N-terminal ATP-binding site of the Hsp90–GA complex indicates that it is a 15 Å deep cone/pyramidal shape pocket, 12 Å in diameter at the top surface and 8 Å wide midway of the pocket.[44] The nature of the binding site is described as a combination of polar and hydrophobic natures imparted by 17 amino acids lining the interior of the pocket, with increasing hydrophobicity down to the bottom of the pocket, except induced polarity (negative electrostatic potential) due to the amino acid Asp93 and a polar residue Thr184, which are found to be crucial for making ligand–protein polar-bonding interactions. The surface of the binding site is mostly polar (positive electrostatic potential) with polar residues, Lys 58 and Lys 112, important for making polar interactions with the ligand. The pyridyl moiety of **PY3** is directed toward the adenine-binding pocket of the natural substrate ADP at the bottom of the site, making crucial H-bonding interactions with amino acids Asp93 and Ser52 (Figure 2).[45] A similar interaction was found with the carbamate residue of GA with Asp93, which is likely to be a crucial interaction amongst the Hsp90 inhibitors. In addition, the pyridyl "NH" of **PY3** makes another important polar interaction with Ser52, which was observed with the OH-resorcinyl moiety of NVP-AUY922 and the carbamate of GA, suggesting that Asp93 and Ser 52 are important residues for protein–ligand interactions.[21] A polar 'NH' of the heterocyclic ring is an essential pharmacophoric feature for ligand binding in the design of Hsp90 inhibitors. The central pyrazoline ring of **PY3** overlaps the ribose sugar pocket of bound ADP and the 5-phenyl ring of **PY3** is oriented toward Phe138, creating hydrophobic stacking interactions. The 4″-OH group of the

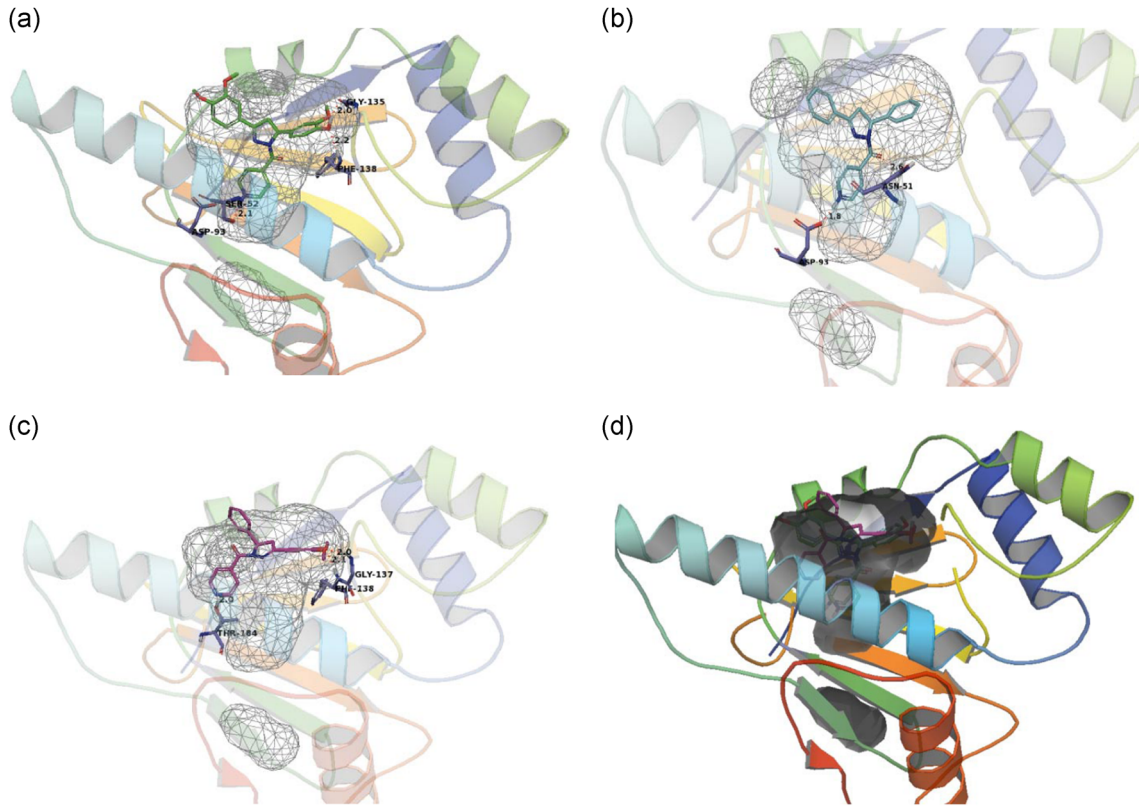


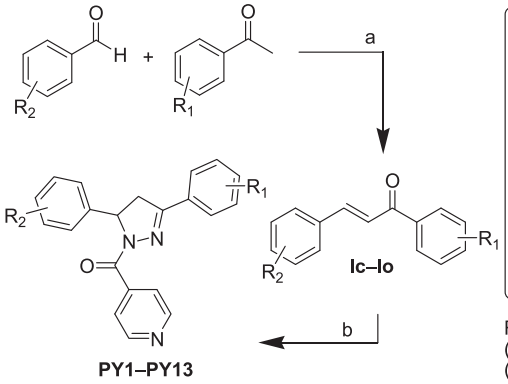
FIGURE 2 Binding interactions of **PY1–PY3** in the adenosine triphosphate-binding site (mesh or surface representation) of Hsp90 protein (cartoon shape; PDB ID: 1YET). (a) H-bonding interactions of green-colored stick form **PY3** with blue colored stick forms of Asp 93 (2.1 Å), Ser 52 (2.1 Å), Phe 138 (2.2 Å), and Gly 135 (2.0 Å). (b) H-bonding interactions of cyano colored stick form **PY1** with Asp 93 (1.8 Å) and Asn 51 (2.6 Å). (c) H-bonding interactions of purple-colored stick form **PY2** with Thr 184 (2.0 Å), Phe 138 (2.1 Å) and Gly 137 (2.0 Å). (d) Overlap of stick forms of **PY3** (green color), **PY1** (cyano color), and **PY2** (purple color) in the active site of Hsp90 protein (cartoon shape; PDB code 1YET)

phenyl ring makes another H-bonding interaction with Gly135, stabilizing the complex, which is found in proximity to the planar amide group of GA. Ligand **PY1** showed hydrogen bonding interactions with Asp93 and Asn51; the latter is in proximity to the Ser52, making important H-bonding interactions. Ligand **PY3** shows a polar H-bonding interaction with Thr184, similar to carbamate of GA, establishing that Asp93, Thr 184, Ser52 are very crucial for protein binding. Ligand **PY2** interacts with Thr184 and a stabilizing interaction with amino acids Gly137 and Phe 138. Ligand **PY4** shows a slightly different orientation in the ADP-binding site, without any significant interaction with Asp93, Ser52, or Thr184, due to bulkiness in its molecular structure and slightly greater rotational penalty (0.3), yet making important hydrophobic interactions with amino acids Val150, Leu107, Val136, Val186, Ala55, Met98, and ranks below the lead molecules. **PY5** interacts with Asp93 with an H-bond parameter of −0.9 and hydrophobic interactions with amino acids Ala55, Phe138, Gly135, Val136, Leu107, suggesting it to be moderately binding in the active site. **PY6** interacts in a similar way with Asp93, but the molecule is slightly low on the polar H-bond parameter (−0.6), suggesting it is a weakly binding ligand in docking analysis and cytotoxicity study. Although ligand **PY7** found to have a hydrogen bond with Asp93, it has low electrostatic interactions and therefore has low binding affinity than **PY1**, **PY2**, and **PY3**. **PY8**, **PY9**, **PY10, PY11**, and **PY13** do not show any significant interaction with a crucial amino acid Asp93 and hence, are placed down the table in terms of binding affinity, which corroborates with the cytotoxicity assay. Although **PY12** has significant interaction with Asp93, it is ranked low in the cytotoxicity assay and docking analysis as the molecule possesses greater rotational flexibility and a greater number of binding poses with a greater scope for nonselectivity.

The SAR analysis of pyrazolines alludes to the importance of a trisubstituted pyrazoline scaffold with a heterocyclic "NH" oriented toward the bottom of the binding pocket (adenine-binding site of ADP) as an important pharmacophore. The presence of polar OH/OCH_3 at the 3′,4′/3″,4″-positions of the benzene ring contribute toward stabilizing interactions of protein–ligand complex, increasing the polar and electrostatic parameters for the drug-like molecules, whereas electronegative atoms do not alter any binding affinity. Aromatic rings at the 3,5-position of the pyrazoline and the heterocyclic aromatic ring at the 1-position of pyrazoline are crucial for nonpolar interactions with hydrophobic residues of the protein. Heterocyclic pyrazoline is essential for projecting the pharmacophoric features for essential interactions with vital amino acids. To further evaluate the polar interactions in the ATP-binding site of Hsp90, docking simulations were performed with different crystal complexes of Hsp90 protein available in the protein data bank (PDB:ID 2BYH, 1OSF, and 4EGK).[39,46,47] Polar interactions of the PY series are given in Table S4.

2.2 | CHEMISTRY

The synthetic protocol of *N*-pyridoyl-Δ^2-pyrazolines (depicted in Scheme 1) began with a Claisen–Schmidt reaction between various substituted benzaldehydes and substituted acetophenones to form 1,3-diphenyl-prop-2-enone derivatives (**Ic–Io**). Purification of 1,3-diphenyl-prop-2-enones was done by flash chromatography in the yields 72–85%. Subsequently, the nucleophilic addition reaction of isonicotinic acid hydrazide with the individual 1,3-diphenyl-prop-2-enones in glacial acetic acid (as solvent), yielded cyclized pyrazolines (**PY1–PY13**) in 25–35%. The structures of the final *N*-pyridoyl-Δ^2-pyrazoline compounds (**PY1–PY13**) were confirmed by ^{1}H-NMR studies, and all the compounds were found to have three characteristic peaks of a doublet of doublets (dd) around 3.2–3.3, 3.7–3.8, and 5.6–5.8 ppm (parts per million), due to J_{abx} coupling of protons on the pyrazoline ring. The infrared (IR) and mass spectral data also confirmed the structural details of *N*-pyridoyl-Δ^2-pyrazoline compounds (**PY1–PY13**). A single crystal of **PY1** was obtained by recrystallization from chloroform at room temperature (22 to 24°C). X-ray diffraction of **PY1** was measured using radiation of wavelength 0.71073 Å at 296 K (Figure 3). The crystal system and space group were found to be monoclinic and P2(1)/c (detailed crystallographic information is given in Tables S5 and S6). The C5–N1 bond is found to be 1.288(3) Å, representing unsaturation (C═N) as compared to C13-N2 (saturated bond, C–N), with a bond length of 1.387(3) Å, confirming it to be a pyrazoline heterocycle. The C6–O1 bond length observed was 1.221 Å, depicting a C═O system. The bond length of the C═N system (C9–N3 and C20–N3) for the pyridyl ring was found to be 1.316(4) and 1.323(4) Å. The bond length for N1 and N2 was observed to be 1.387(3) Å (data pertaining to the X-ray diffraction studies of **PY1** can be



PY1: R_1 = H; R_2 = H
PY2: R_1 = 3',4'-OCH_3; R_2 = H
PY3: R_1 = 3',4'-OCH_3; R_2 = 4''-OH, 3''-OCH_3
PY4: R_1 = 2',4'-OCH_3; R'' = 4''-$OCH_2C_6H_5$, 3''-OCH_3
PY5: R_1 = H; R'' = 4''-$OCH_2C_6H_5$, 3''-OCH_3
PY6: R_1 = 3',4'-OCH_3; R'' = 3'', 4''-OCH_3
PY7: R_1 = 4-Cl; R_2 = 3'', 4''-OCH_3
PY8: R_1 = 2',4'-OCH_3; R_2 = 4''-$OCH_2C_6H_5$
PY9: R_1 = H; R_2 = 4''-$OCH_2C_6H_5$
PY10: R_1 = H; R_2 = 4''-Cl
PY11: R_1 = 2',4'-OCH_3; R_2 = 4''-Cl
PY12: R_1 = 2',4'-OCH_3;R_2 = 4''-$OCH_2C_6H_4$(P)F
PY13: R_1 = H; R_2 = 4''-$OCH_2C_6H_4$(P)F

Reagents and conditions:
(a) NaOH, MeOH, RT stirring for 12 hr
(b) Isonicotinic acid hydrazide, GAA, reflux for 12 hr

SCHEME 1 Synthesis of *N*-pyridoyl-Δ^2-pyrazoline analogs (**PY1–PY13**)

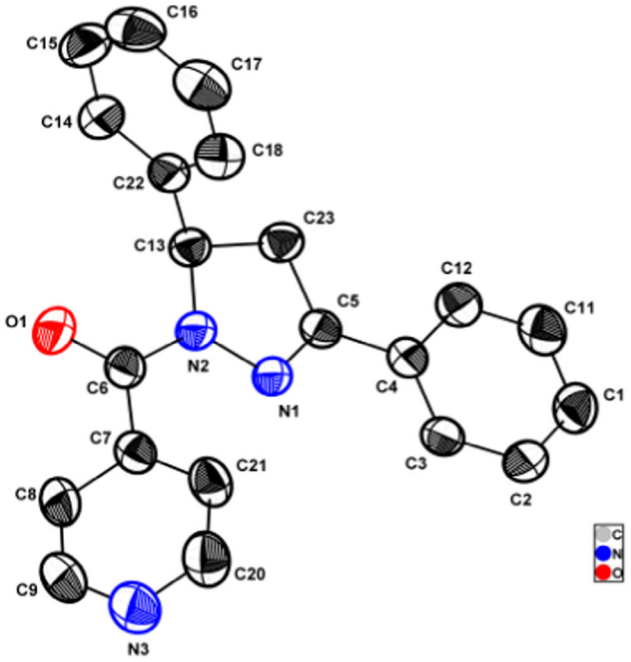


FIGURE 3 Oak ridge thermal-ellipsoid plot program (ORTEP) diagram from X-ray crystalographic study of **PY1**

accessed through the Cambridge Crystallographic Data Center [CCDC] with the deposition number 1533986).

2.3 | In vitro cell proliferation assay

To evaluate the biological activity of the **PY** series, anti-proliferative activity screening by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay method was performed against human breast cancer cells MDA-MB-468 and human melanoma cells A375.[48] The activities of the *N*-pyridoyl-Δ^2-pyrazoline compounds (**PY1–PY13**) were compared with the reported Hsp90 inhibitor NVP-AUY922. **PY1–PY3** turned out to be the promising compounds among the series against breast and melanoma cancer cells (Table 1). The results suggest that **PY1–PY3** exhibited differential effects between cell lines of human breast cancer (MDA-MB-468) and human melanoma (A375). Compounds **PY1–PY3** exhibited a robust cytotoxic effect against human breast cancer with a range of IC_{50} values from 1.6 to 12 μM. Compounds **PY1–PY3** were also found to have significant cytotoxic activity against human melanoma cells with a range of IC_{50} values from 7.7 to 22 μM.

2.4 | Proteomic analysis

On the basis of the results of in vitro antiproliferative studies on human cancer cells, we carried out the proteomic analysis of hit compounds **PY1–PY3** to explore the Hsp90 protein interaction. Drug-affinity responsive target stability (DARTS), a recent proteomics approach to investigate small-molecule binding to targets using protease-based digestion, was performed on the cell lysates of human breast cancer (MDA-MB-468).[49] The DARTS assay demonstrated that **PY1–PY3** protect Hsp90β from protease digestion similarly to RAD (see the 1/1,000 pronase dilution in Figures 4 and 5). The protection of Hsp90 against proteolysis is possible only because of the stable Hsp90-ligand complex formed by PY compounds. RAD also protects the Hsp90 protein against proteolysis. Untreated cell lysates failed to show the band of Hsp90, as the Hsp90 was proteolyzed by pronase to fragments. The in silico docking studies corroborate with the DARTS analysis, signifying that **PY1–PY3** interacts with Hsp90, and therefore shows promising antiproliferative activity.

3 | CONCLUSION

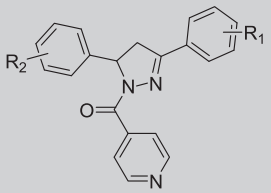
In conclusion, the drug design, chemical synthesis, and biological evaluation of *N*-pyridoyl-Δ^2-pyrazolines are reported. The molecular modeling and docking simulations predicted the binding potential of the PY series in the N-terminal ATP-binding pocket of Hsp90. PY series have crucial polar interactions with the important residues of Hsp90, such as Asp93 and Thr184. In addition, nonpolar hydrophobic interactions were also responsible for the efficient binding of **PY1–PY3** with Hsp90, which is evident by an admirable docking score (−10.2 to −8.1 kcal/mol). Compounds **PY1** and **PY2** significantly reduced the human breast cancer cell proliferation (IC_{50} 1.60 and 2.8 μM), whereas **PY3** was moderate in action (IC_{50} 12 μM). Compound **PY1** was also found to be a promising inhibitor of human melanoma cells (IC_{50} 7.7 μM). Proteomic investigation in breast cancer cells implies the Hsp90 binding property of **PY1–PY3** molecules. All these investigations propose *N*-pyridoyl-Δ^2-pyrazolines **(PY1–PY3)** as promising anticancer compounds showing Hsp90 inhibition and show potential for further development as effective anticancer agents.

4 | EXPERIMENTAL

4.1 | Molecular modeling and docking simulations

Molecular docking simulations were carried out on the Dell workstation T1500 with the Windows 7 operating system using Schrodinger Maestro 9.1 drug design software.[43] The Hsp90 protein bound with GA (PDB ID: 1YET)[44] was downloaded from the RCSB Protein Data Bank for drug design studies. The protein was prepared by filling missing loops and missing side chains using a protein preparation wizard application of the Schrodinger software. Chain A of Hsp90 protein was further processed by removing nonreactive water molecules and crystal ligand (GA). The ionized protein having the lowest penalty was energy-minimized using the optimized potential for liquid simulations 2005 force field incorporated in the Impref tool of Glide programme to finally prepare processed 1YET protein. The grid was generated in the processed protein by excluding the docked ligand in the active site using a receptor grid generation tool of the Glide programme (the van der Waals radius-scaling factor was limited to 1.0 with a partial charge cut-off of 0.25). The active site was also predicted using DoGSiteScorer

TABLE 1 Physical properties and anticancer activity of *N*-pyridoyl-Δ^2-pyrazoline analogs (**PY1–PY13**)



PY1–PY13

Compound	R_1	R_2	Yield (%)	m.p. (°C)	IC_{50} (μM) ± SEM[a]	
					MDA-MB-468[b]	A375[c]
PY1	H	H	55	310	1.60 ± 0.06	7.73 ± 0.04
PY2	3′,4′-OCH_3	H	65	124	2.84 ± 0.05	15.45 ± 0.03
PY3	3′,4′-OCH_3	4″-OH, 3″-OCH_3	73	157	12.05 ± 0.03	22.10 ± 0.48
PY4	2′,4′-OCH_3	4″-$OCH_2C_6H_5$, 3″-OCH_3	60	127	45.80 ± 0.06	47.25 ± 0.04
PY5	H	4″-$OCH_2C_6H_5$, 3″-OCH_3	65	147	45.10 ± 0.03	49.10 ± 0.12
PY6	3′,4′-OCH_3	3″,4″-OCH_3	75	155	35.72 ± 0.03	48.87 ± 0.13
PY7	4′-Cl	3″,4″-OCH_3	74	157	34.75 ± 0.15	40.32 ± 0.13
PY8	2′,4′-OCH_3	4″-$OCH_2C_6H_5$	66	177	38.58 ± 0.16	35.87 ± 0.24
PY9	H	4″-$OCH_2C_6H_5$	70	127	46.87 ± 0.23	43.57 ± 0.43
PY10	H	4″-Cl	75	150	48.68 ± 0.14	47.50 ± 0.18
PY11	2′,4′-OCH_3	4″-Cl	68	157	44.35 ± 0.34	48.57 ± 0.34
PY12	2′,4′-OCH_3	4′-$OCH_2C_6H_5$(P)F	73	144	37.59 ± 0.43	47.59 ± 0.26
PY13	H	4″-$OCH_2C_6H_5$(P)F	75	138	36.68 ± 0.37	38.98 ± 0.13
NVP-AUY922	–	–	–	–	0.012 ± 0.01	0.021 ± 0.03

Abbreviations: SEM, standard error of the mean; m.p., melting point.
[a]Data represent the IC_{50} values for a 3-day exposure to normalized to no drug controls and is the mean of triplicate experiments performed; concentration ranges for **PY1–PY3** compounds were 3.12 to 50 μM and for NVP-AUY922 12.5 to 200 nM.
[b]Human breast cancer.
[c]Human melanoma.

software.[41] The ligands were subjected to Ligprep simulations to generate energy-minimized three-dimensional structures (300 steps) by investigating tautomeric, stereochemical, and ionization variations. The ligprep out ligands were docked flexibly in the protein grid using Glide-extra precision (XP) simulations. Compounds having ≤300 atoms and ≤50 rotatable bonds were docked using five poses per ligand and 10,000 poses per docking run. Energies of residues within 12 Å of grid were used for simulations. Poses having coulomb–vdW energy greater than 0.0 kcal/mol and poses having an RMS deviation of 0.5 Å were discarded.[42] Finally, the docked ligands were scored based on the

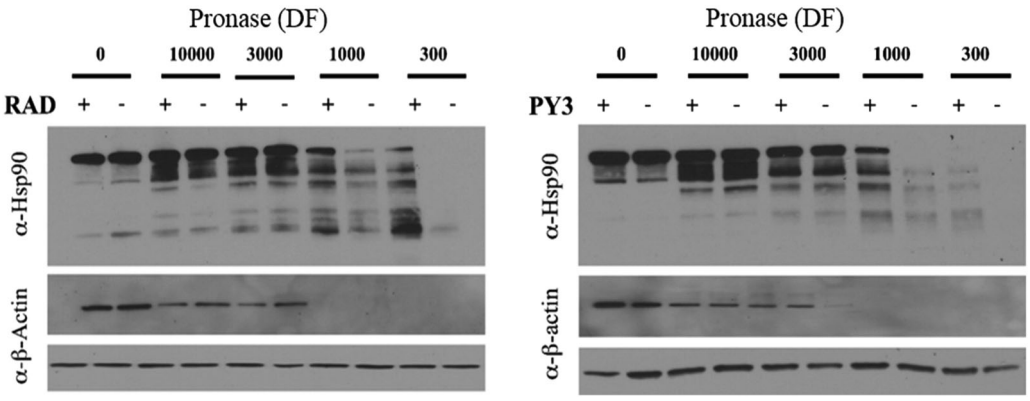


FIGURE 4 Proteomic analysis of RAD and **PY3** mediated protection of Hsp90 in MDA-MB-468 lysate. One millimolar RAD and **PY3** protect Hsp90 from pronase degradation. Middle β-actin blot demonstrates the compound effect is specific for Hsp90 because of the equivalent proteolysis (+/−) compound. Bottom β-actin is a loading control from nonproteolyzed samples run simultaneously on a separate gel. Concentrations of pronase used are 1/10,000, 1/3,000, 1/1,000, and 1/300. DF, dilution factor; RAD, radicicol

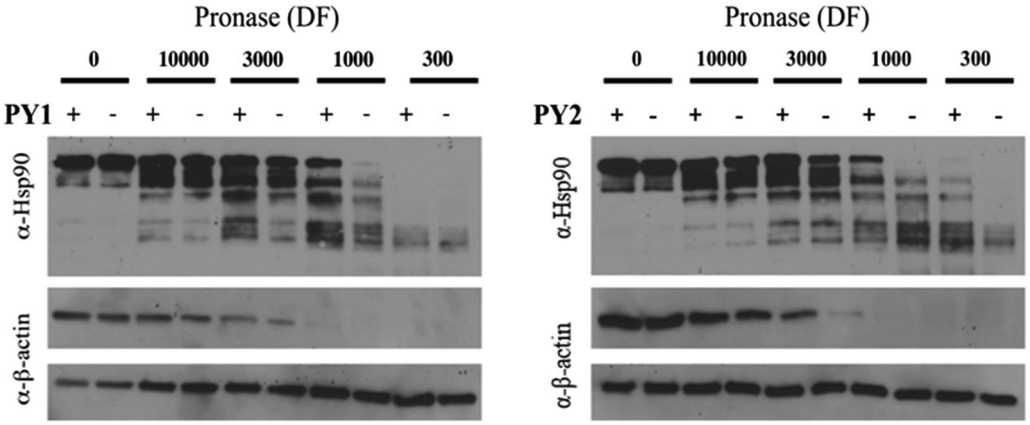


FIGURE 5 Proteomic analysis of **PY1** and **PY2** analog mediated protection of Hsp90 in MDA-MB-468 cell lysate. One millimolar **PY1** and **PY2** protect Hsp90 from degradation. The specificity of this effect is indicated by equivalent β-actin degradation (+/−) compound (middle blot). The bottom β-actin blot acts as a loading control from the same sample but without proteolysis. Concentrations of pronase used are 1/10,000, 1/3,000, 1/1,000 and 1/300. DF, dilution factor

nonbonded interactions, such as lipophilic pair term, hydrogen bonding, hydrophobic enclosure reward, and electrostatic rewards.

Active site prediction for Hsp90, validation of docking methodology, extra precision (XP) docking results of Maestro 9.1 Glide, comparative docking interactions of the ligands in different crystal structures of Hsp90 protein, and crystallographic information of PY1 are provided as Supporting Information.

4.2 | Chemistry

^{1}H-NMR spectra were recorded in $CDCl_3$ on a Bruker Avance 300 MHz NMR spectrometer (Bruker BioSpin AG, Fallanden, Switzerland); chemical shifts (δ) were reported in ppm with tetramethylsilane as an internal standard. Mass fragmentation was recorded on an API2000 LC/MS mass spectrometer (Bruker Daltonics Inc., Billerica, MA). X-ray diffraction studies were done using Bruker-APEX III (X-ray diffractometer). Column chromatography was performed on Buchi flash chromatography with C-601 Pump Module, Pump Controller C-610, and Glass Column 26/230 cpl using silica gel (100–200 mesh). Infrared spectra were obtained from FT-IR-Affinity-1 spectrometer (Shimadzu, Japan). Uncorrected melting points were determined on an electrothermal melting point apparatus. Unless otherwise noted, all solvents and reagents were commercially available and used without further purification. The spectroscopic characterizations and original spectra of the synthesized compounds are provided in the Supporting Information.

4.3 | Biological activity

4.3.1 | Cell antiproliferative activity assay

The growth inhibitory activity of the test compounds was determined by MTT assay against human breast MDA-MB-468 and human melanoma A375 cells.[48] Each cell line was seeded on 96-well microplates at a density of 1.0×10^4 cells/well in 80 μl and allowed to attach to the tissue culture-treated plastics after placing the 96-well plate in a Nuncoverplate for evaporation control for 4 hr. A five-step, two-fold drug dose dilution series was prepared robotically in a Biomek 3000 (Beckman Coulter) in the medium described previously. The test compounds were delivered as 20-μl aliquots mixed into 80-μl cell aliquot for a final exposure concentration. A Day-0 plate for each cell line was developed by the robotic addition of 10 μl of 5 mg/ml MTT (in DMEM [Dulbecco's modified Eagle's medium], low glucose, 0% fetal bovine serum, and without phenol red) per well and allowed to develop for 4 hr after being placed in a Nuncoverplate to control evaporation. Then, 100 μl of MTT solvent (0.1 N HCl in anhydrous isopropanol with 10% Triton X-100) was added, the assay plates were tightly wrapped in foil and placed in sealed zip lock bags to allow the solubilization of the MTT formazan product to occur and progress to solubilization for reading in a spectrophotometer at 570 nm. The subtraction of background absorbance measured at 690 nm was not performed. The Day-3 test plates were developed as described above. IC_{50} values were calculated using GraphPad Prism (Version 5.02, GraphPad software).

The InChI data of the PY series with anticancer activity against MDA MB468 and A375 cell lines are provided as Supporting Information.

4.3.2 | Hsp90–small-molecule inhibitor DARTs assay using whole-cell lysate[49]

MDA-MB-468 cells were lysed with lysis buffer (1 mM $NaVO_3$, 50 mM HEPES [4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid], pH 7.4, 100 mM NaCl, 0.5% NP40, 1 mM EDTA [ethylenediaminetetraacetic acid], 1 mM EGTA [ethylene glycol-bis(β-aminoethyl ether)-*N*,*N*,*N*′,*N*′-tetraacetic acid], 50 μg/ml RNase, 1% Triton X-100, 1% deoxycholic acid, 1 μg/1 μl leupeptin or Roche protease inhibitor mixture and 1× protease mixture) for 15 min at 25°C. After centrifugation (13,200 rpm using Eppendorf microcentrifuge 5415D; 15 min), the protein concentration of the lysate was measured using MicroBCA™ protein assay kit. Twenty-five

micrograms of protein cell lysate was incubated with 1 mM compound and binding buffer (50 mM Tris HCl pH 8.0, 50 mM NaCl, 10 mM $CaCl_2$) to a 20-μl final volume for 2 hr at room temperature. Samples were digested with Pronase (Roche) at varying dilutions for 15 min at 25°C. The reaction was stopped by the addition of 5 μl of 5× sodium dodecyl sulfate (SDS) loading dye and this was immediately followed by boiling samples at 95°C for 5 min. Samples were run in 4–15% gradient SDS-PAGE (SDS-polyacrylamide gel electrophoresis) gels at 150 V for 60 min followed by Western blot analysis. An equal aliquot of the nonproteolyzed sample was run simultaneously on a separate gel to assess β-acting levels as a loading control. Blots were probed with anti-Hsp90 antibody (ADI-SPA-831; Enzo Life Sciences). The blots were stripped and reprobed with anti-β-actin antibody (JLA20; DSHB University of Iowa) to demonstrate that the β-actin was proteolyzed equally in the presence or absence of compound, and hence the compound-mediated protection of Hsp90 was specific. The same anti-β-actin antibody was used to probe β-actin levels in the loading control gel.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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COMPREHENSIVELY EXAMINING IMPURITY PROFILES IN PHARMACEUTICALS: A REVIEW

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Abstract - Any substance that coexists with the original drug, such as starting material, intermediates, or that is formed as a result of any side effects, is considered an impurity. There are three kinds of impurities: Impurities that are closely related to the product and originate from the chemical or biosynthetic route themselves, impurities that are formed when the drug spontaneously decomposes while being stored or exposed to extreme conditions, or impurities that may be present in the final product as precursors. Selective methods should be used to identify and quantify impurities greater than 0.1%. The final evidence for the impurities' previously determined structures, which can be synthesized from their suggested structures, will be provided. Hence it is fundamental for know the design of these pollutants in the mass medication to modify the response condition and to decrease the amount of debasement to a satisfactory level. We are able to obtain a pure substance with less toxicity and greater safety in drug therapy thanks to the isolation, identification, and quantification of impurities. New drug substance impurity research is covered in this overview.
Keywords: New drugs, toxicity, and impurities.

1 INTRODUCTION

Utilizing appropriate chromatographic, spectroscopic, and analytical methods, a general plan is established for estimating the impurity of bulk drug substances. The various requirements for a drug substance's impurity profile are discussed. Any substance that coexists with the original drug, such as starting material, intermediates, or that is formed as a result of any side effects, is considered an impurity. Even a trace amount of these undesirable chemicals could have an impact on the safety and efficacy of pharmaceutical products. Regulators are now paying close attention to impurity profiling, or the identification and quantity of impurities in pharmaceuticals. The various pharmacopoeias, including the British Pharmacopoeia (BP), the United States Pharmacopoeia (USP), and the Indian Pharmacopoeia (IP), are gradually introducing limits on the permissible levels of impurities found in APIs or formulations.

1.1 Types of Impurity

During their manufacturing processes, organic and inorganic medicinal substances are identically contaminated. Since the natural substances have a place with an extremely extensive variety of compound gatherings and simultaneously the sullying debasements being of differed nature

the errand of distinguishing the pollutions turns into a troublesome work. As a result, organic medicinal compounds' contaminating impurities can be divided into the following categories:

- Inorganic impurities
- Organic contaminants
- Chemical intermediates' contamination,

Impurities that are closely related to the product and originate from the chemical or biosynthetic route themselves, impurities that are formed when the drug spontaneously decomposes while being stored or exposed to extreme conditions, or impurities that may be present in the final product as precursors.

Selective methods should be used to identify and quantify impurities greater than 0.1%. The final evidence for the impurities' previously determined structures, which can be synthesized from their suggested structures, will be provided. Hence it is fundamental for know the design of these pollutants in the mass medication to modify the response condition and to decrease the amount of debasement to a satisfactory level. We are able to obtain a pure substance with less toxicity.

These impurities could be quantified in a way that could be used for drug substance validation and quality control. Administrative specialists like US FDA, CGMP, TGA, and MCA demand the debasement profiling of medications. There are two ways to deal with impurities in new drug substances: (1) the chemical aspect, which includes the classification and identification of impurities, the generation of reports, a brief discussion of analytical procedures, and a listing of impurities in specifications; and (2) the safety aspect, which includes specific guidance for quantifying impurities that are present in a drug substance used in clinical studies at significantly lower levels.

1.2 Organic Impurities

Based on a sound scientific evaluation of the chemical reactions involved in the synthesis, it is necessary to summarize the actual and potential impurities that are most likely to occur during the synthesis, purification, and storage of the drug substance. This includes impurities associated with raw materials that may contribute to the impurity profile of the drug substance. Test results from materials produced during the development process and batches from commercial processes are examples of the laboratory studies carried out to identify impurities in the drug. It is necessary to contrast the impurity profile of the drug lots intended for marketing with that of those used in development. The studies using spectroscopy (NMR, IR, MS, etc.) directed to portray the design of genuine pollutants present in the medication substance over a clear degree of 0.1% (e.g., determined utilizing the reaction element of the medication substance) ought to be depicted. All repetitive pollutions over an evident degree of 0.1% in bunches produced by the proposed business cycle ought to be distinguished of these examinations.

1.3 Inorganic Impurities

Inorganic impurities are normally detected and quantified using Pharmacopeial or other appropriate standards. Carryover of catalysts to

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the drug substance should be evaluated during development.

1.4 Residual Solvents

The control of residues of solvents used in the manufacturing process for the drug substance should be discussed. Acceptance criteria should be based on Pharmacopeial standards, or ICH guidelines or known safety data, depends on the dose, duration of treatment, and route of administration.

2 SOURCES OF PHARMACEUTICAL IMPURITY

Pollutants related in with APIs Natural debasements, Inorganic contaminations, Dissolvable deposits Pollutants connected with definition Pollution structures during plan, Development of contaminations on maturing. The formulated forms of active pharmaceutical ingredients are medicines. Medicines contain two kinds of impurities: 1) Impurities that are associated with active pharmaceutical ingredients; and 2) Impurities that form during formulation, during aging, or in connection with the forms that are formulated.

2.1 Degradation Products

During the production of bulk drugs, degradation of the finished product can also result in the formation of impurities. However, common impurities in medicines include degradation products that result from aging, storage, formulation to various dosage forms, or both. The debasement of penicillins and cephalosporins is a notable illustration of corruption items. Their degradation is greatly influenced by the C6/C7 side chain's presence of an a-amino group and a ß-lactam ring.

Reagents, ligands, and impetuses These synthetics are less ordinarily tracked down in APIs; However, they may occasionally present an issue as contaminants.

In general, a single API may contain all of the aforementioned kinds of organic impurities in quantities that range from negligible to significant. Both the manufacturers and the various research groups conducted an in-depth investigation of the impurities found in semi-synthetic penicillin. Methods for isolating, detecting, and quantifying degradation products and antigenic polymeric by-products are described in a review paper on penicillins and cephalosporins. The API contains traces of ampicillin polymers and hydrolyzed products, according to studies. Additionally, it has been discovered that the product degrades when certain chemicals, like triethylamine, are present. Accelerated stability testing revealed that ampicillin trihydrate samples with a triethylamine content of between 2000 and 4000 ppm, as determined by the visual color method developed by Gist-Brocades, Delft, Holland, were stable. However, when the triethylamine content reached 7000 ppm, the product showed significant degradation. Limit tests for the traces of impurities found in bulk raw materials of ampicillin and amoxycillin were included in the most recent pharmacopoeia. As organic impurities are the most prevalent product- and process-related impurities, it is the responsibility of both API manufacturers and users (i.e. formulators) to manage these impurities in accordance with ICH

guidelines or compendia. The residual solvents associated with these APIs have also been identified.

3 APPLICATIONS

In the areas of drug design and quality, stability, and safety monitoring of pharmaceutical compounds, whether produced synthetically, extracted from natural products, or recombinantly, numerous applications have been sought. Alkaloids, amines, amino acids, analgesics, antibacterial, anticonvulsant, antidepressant, tranquilizers, antineoplastic agents, local anesthetics, macromolecules, steroids, and a variety of other applications are among them.

Synthetic dyes, which are frequently added to a great number of foodstuffs and are generally preferred to natural colors largely due to their greater stability along the production industrial process, are a recent area of interest in the food chemistry devoted to the protection of human health. The use of artificial color in food has a long history. Both vegetable extracts and "unnatural" color were used in food and drink in the 18th and 19th centuries. Lead chromate, mercuric sulfide, lead oxide, and copper arsenite, for instance, were used to color sweets. These metallic compounds were no longer used thanks to legislation and newly developed chemically synthesized dyes. In comparison to natural dyes, synthetic dyes were significantly brighter, less expensive, more uniform, more stable (in their reactions to high processing temperatures, acids, carbon dioxide, storage, and light), more potent (i.e., less could be used to achieve the same effect), and offered a wider range of shades. The toxic properties of new dyes became apparent as their use grew in popularity. The use of synthetic dyes has increased since then, but our awareness of their toxicity has also increased.

Ascorbic acid (vitamin C) and sodium benzoate are found in a lot of drinks. There is a strong possibility that a chemical reaction will take place when Vitamin C and benzoate salts come into contact with high levels of light and/or heat. This procedure produces benzene. Benzene development might happen at part per billion (micrograms per kilo) levels in some drink formulations. To ensure the food's microbiological safety, sodium benzoate can be added to many foods as a permitted food preservative. Additionally, ascorbic acid can be added to beverages as an approved food additive (antioxidant). Fruit and fruit juices naturally contain it as well. Ascorbic acid creates hydroxyl radicals when it interacts with water-soluble metals like copper and iron. These hydroxyl radicals then combine with benzoic acid to produce low levels of benzene. Beverages in which benzoic acid and ascorbic acid are purposefully added to ensure the safety of microorganisms are likely to have higher levels of benzene.

3.1 General Scheme for Drug Impurity Profiling

The first step in impurity profiling is to find the impurities using a gas chromatogram, thin-layer chromatogram, or high-performance liquid chromatogram. Standard impurity samples from synthetic organic chemists, such as the last intermediate of the synthesis, products of predictable side reactions,

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degradation products if any, and so on. If standard samples don't work, the best way to figure out the impurity's structure is to look at the UV spectra, which are easy to get with a diode-array detector in HPLC and a densitometer, and then figure out how much of each one there is. NMR spectral data can be used to generate the impurity's structure in rare instances with complete knowledge of drug martial synthesis. The mass spectrum of the impurity is taken as the next step in the process of impurity profiling if the information obtained from the UV spectrum is insufficient. The major drawback of matching the synthesized material with the impurity in question in the manner described above is the impurity's volatility and thermal stability, which limits the use of spectroscopic techniques in drug impurity profiling without chromatographic separation. Derivatization reactions, which are frequently used in GC/MS analysis, pose a problem due to the possibility that the derivatization reaction's side products will be confused with the impurities. The material (impurity standard) and proposed structure are synthesized in the following impurity profiling step. As previously mentioned, the synthesized material is retained and matched spectrally to the impurity in question. It is also important to note that spectroscopic methods can be used for drug impurity profiling without chromatographic separation. A fingerprint picture of the sample's purity can be obtained from spectra produced by mass spectrometers and high-resolution, highly sensitive NMR spectrometers equipped with APCI and ESI facilities. Identification of new or more significant levels of a GTI in the FDC item contrasted and the single-substance Programming interface item, or an underlying GTI evaluation that reveals possible GTIs in a showcased item, may bring about extra administrative examination of that item, especially in the event that a GTI appraisal has not been recently directed on that item. This may necessitate the implementation of additional process controls or even the temporary suspension of distribution while the remaining issues are addressed.

4 CONCLUSION

During the synthesis of drug substances and the production of dosage forms, impurity profiling is very important because it can provide crucial information about the toxicity, safety, various limits of detection, and limits of quantitation, of several organic and inorganic impurities that typically accompany bulk drugs and finished products. The impurity profiling process is made simple by the precise method development and procedure validation.

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A REVISED APPROACH FOR EXTRACTING RHEIN FROM SENNA

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Abstract - The hydrolysis of the sennosides and the extraction of the hydrolysis products (free anthraquinones) are carried out in one step in a straightforward and effective method for isolating rhein from Cassia angustifolia (senna) leaves. The anthraquinone mixture is used to isolate rhein once more. When compared to more traditional approaches, this one requires fewer steps to isolate rhein than other methods.

Keywords: Aloe-emodin, Sennosides, Rhein, and Cassia angustifolia.

1 INTRODUCTION

In the free state and as a glucoside, Rhein (1, 8-dihydroxyanthraquinone-3-carboxylic acid) can be found in Rheum species' senna leaves; and also in a number of Cassia species[1]. Due to its antiviral, antitumor, and antioxidant properties, Rhein is currently a topic of interest. Additionally, it is utilized as a starting material for the synthesis of diacerein (fig. 1,8-diacyl derivative). 1), which is helpful in treating osteoarthritis and has anti-inflammatory properties. Rhein from indigenous plant sources must therefore be extracted in a straightforward and effective manner. Oxidative hydrolysis of aloin, a C-glycoside found in Aloe species, to obtain aloe-emodin, acetylation of aloe-emodin, and chromic oxidation of the acetylated product to obtain diacerein is currently the preferred method for the synthesis of diacerein[2].

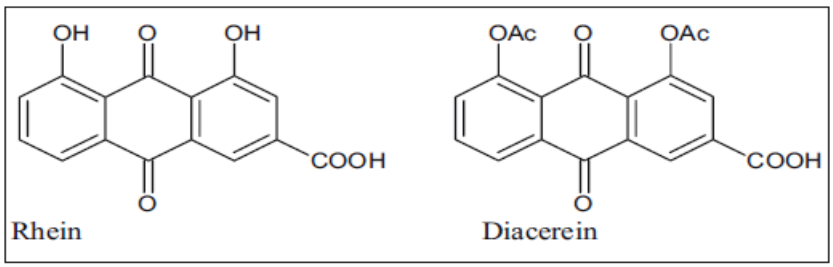

Fig. 1 Rhein and its 1,8-diacyl derivative (diacerein)

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Senna (Cassia angustifolia) is a little bush that is generally developed in southern India, essentially in Tamil Nadu. This plant's leaves and pods contain at least 2.5% anthraquinone glycosides, primarily sennosides A and B (fig.). 2), which are aloe-emodin and rhein-derived dianthrone glucosides. Because of this, senna leaf is a significant source of rhein. A straightforward method for separating rhein from senna leaf is described in the following paper.

The Mumbai market served as the source for the C. angustifolia leaves. Sodium hydrogen carbonate and hydrochloric corrosive were of insightful grade and were bought from S. D. Fine Substance Restricted, Mumbai. The leaves were ground up into a powder, and the powdered leaves were used for extraction.

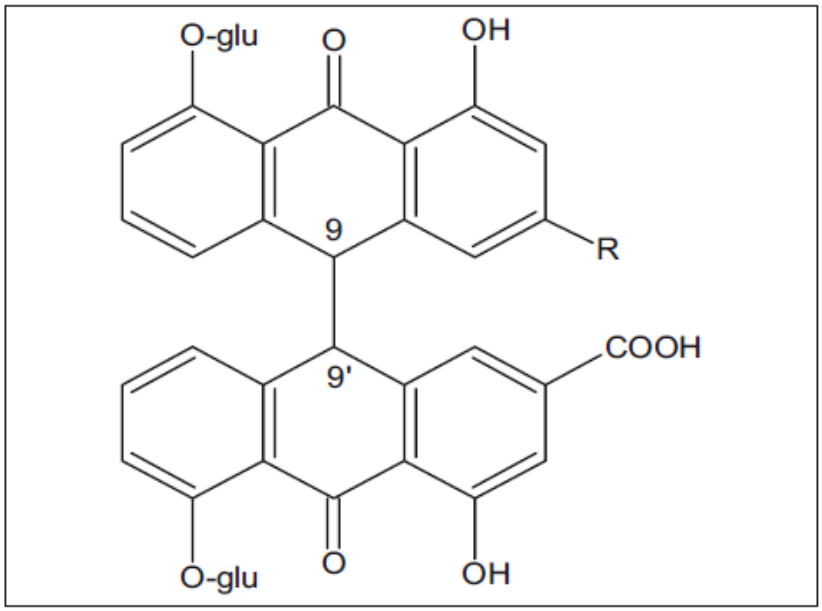

Fig. 2 Anthraquinone glycosides (sennosides) present in senna leaves.

25 grams of powdered senna leaves were mixed with a mixture of 75% water and alcohol. 5 milliliters of hydrochloric acid were added after the mixture was slightly warmed. After incorporating one hundred milliliters of toluene into a biphasic mixture and refluxing it for six hours, the mixture was slightly cooled, filtered to remove any crude drug, and the aqueous and organic layers were separated from one another. To recover any free anthraquinones and combine the toluene layers, the crude drug and aqueous layers were washed with toluene. The pink color of the aqueous layer was removed by partitioning the toluene layer with 10% sodium hydrogen carbonate solution. Hydrochloric acid was

used to acidify the aqueous layer, and ethyl acetate was used to dissolve the precipitate. The product was made from glacial acetic acid after the ethyl acetate layer was evaporated. Chemical tests and spectral studies were conducted on the obtained dark yellow compound to determine its identity. Borntrager's reagent was used to treat the isolated compound in an alcoholic solution (5 percent alcoholic potassium hydroxide); Anthraquinones were found to be present, as evidenced by the pink color.

Using ethyl acetate, thin-layer chromatography was carried out on a precoated silica gel G60 F254 plate (E. Merck): methanol: With water serving as the mobile phase, Borntrager's reagent produced a pink color due to the presence of a single band at Rf 0.3. On a Perkin- Elmer FTIR spectrometer, the isolated compound's infrared (IR) spectrum was recorded. A large peak at 3063 cm-1 (hydroxyl), 1629 cm-1 (chelated carbonyl), and 1696 cm-1 (carboxyl) was observed in the infrared spectra. Mass range, was recorded on a Micromass, Q-TOF MS ES+. The compound's molecular weight was determined by the molecular ion peak at 285 m/e. The UV/Vis range was recorded on a Jasco V-530 UV/Vis Spectrophotometer. Methanol's UV/Vis maxima (nm) were discovered at 228, 258 (for Ar-C=O) and 432 (for the quinonoid group)[5]. In view of substance tests and unearthly examinations, the segregated compound was distinguished as rhein.

On a laboratory scale, it was found that the above-described method of hydrolyzing and extracting anthraquinones in a single step using a biphasic system was effective for isolating rhein. The rhein so acquired can be utilized for the amalgamation of diacerein and different subsidiaries of rhein. This method needs to be improved further in order to be suitable for large-scale extraction.

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UNDERSTANDING THE ROLE OF DRUG MASTER FILES IN THE PHARMACEUTICAL INDUSTRY

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Abstract - A Medication Expert Record is a secret report used to give definite data about offices, cycles or articles utilized in the assembling system, bundling and putting away of at least one human medication. The person who created the Drug Master File can use it to support their application, as can one or more additional parties. A company can comply with regulatory requirements for the disclosure of processing details while protecting its intellectual property from its partner through the Drug Master File filing. The important aspects of filing and processing are covered in the review, which includes various kinds of Drug Master Files.
Keywords: Holder, intellectual property, regulatory requirements, and the drug master file.

1 INTRODUCTION

The Drug Master File, or DMF, is a document that a pharmaceutical manufacturer submits to the appropriate regulatory authority in the intended drug market at its sole discretion. A DMF is typically filed when two or more businesses collaborate on the development or manufacturing of a drug product. The DMF documenting permits a firm to safeguard its protected innovation from its accomplice while following administrative prerequisites for revelation of handling subtleties.

1.1 The Drug Master File (DMF) is a document that contains all of the information regarding an API or finished drug dosage form. In Europe and the United States, it is referred to as the US-Drug Master File (US-DMF) or the Active Substance Master File (ASMF).

Any human drug product's chemistry, manufacturing, stability, purity, impurity profile, packaging, and cGMP status are all covered in detail in the DMF.

2 DEFINITION

A DMF is a submission to the Food and Drug Administration (FDA) of information, typically pertaining to the Chemistry, Manufacturing, and Controls (CMC) of a component of a drug product, in order to enable the FDA to examine this information in support of a third party's submission.

A DMF can contain information about drugs or other things that aren't CMC.

DMF is a submission to the Food and Drug Administration (FDA) that can be used to provide private, detailed information about facilities, procedures, or items used in the production, packaging, and storage of one or more human drugs.

DMF is a submission to the Food and Drug Administration (FDA)

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that can be used to provide private, detailed information about facilities, procedures, or items used in the production, packaging, and storage of one or more human drugs.

3 GENERALLY DMF'S HAVE TWO PARTS:

(1) Applicant's Part: This contains nonconfidential information that the license holder needs to assess for the marketing.

(2) Restricted Part: This contains confidential information about the manufacturing procedure that only needs to be disclosed to the authorities.

3.1 Types of DMF's:

Originally there are five types, they are:

I. Manufacturing Plant Information
II. Drug Substance, Drug Product, Intermediates and material used in their manufacture
III. Packaging
IV. Excipients, Colorant, Flavour, Essence or Materials Used in the preparation
V. Other Sterile Manufacturing Plants, Biotech Contract facilities, clinical, tox

3.2 Current Types of DMF's:

Now four types are present, they are:

I. Drug Substance, Drug Product, Intermediates and material used in their manufacture
II. Packaging Material
III. Excipients, Colorant, Flavour, Essence, or Material Used in Their
IV. Preparation
V. Other Sterile Manufacturing Plants,

3.3 DMF Filing Process:

- The FDA's Central Drug Evaluation and Research (CDRL) receives two copies of the Drug Master File, a signed original of the covering letter, and other necessary documents.
- The nontechnical information will be checked for completeness and suitability for submission by the Drug Master File staff. The staff will attempt to contact the proposed holder to obtain the necessary documents to file the DMF if the essential components are missing.
- A letter is sent to the contact person listed in the DMF when the DMFs are determined to be acceptable for filing by the document room staff.

3.4 Steps for Filing A DMF:

1. The left and right margins of the document should be at least 3/4 inches apart.
2. On standard letter-size paper, print the transmittal page, administrative information, and DMF information. If a diagram or schematic requires a larger sheet of paper, fold it and attach it to a letter-sized page in a way that lets the page be opened and refolded. A DMF should have a maximum thickness of no more than 2 inches for each volume.
3. If there are more than one volume in a submission, divide it by the total number of volumes. For instance, 1 of 3, 2 of 3, and so on.)
4. Sign all documents that need to be signed (only if you are the owner of the DMF or an authorized representative).

5. Collect the document from copies; The FDA expects both from you.
6. Utilizing a standard hole punch, punch documents.
7. A document jacket should be applied to each volume's original and copy.

3.5 DMF File Format:

- The DMF must adhere to the format's specifications. The DMF is submitted as original and duplicate jackets that have been collected, assembled, paginated, and jacketed. The jackets are made from covers that were obtained from the government printing office and are made just for the DMFs.
- Each volume is numbered, and the paper needs to be the standard size.
- Two copies of the DMF, one with a blue cover and one with a red cover, must be submitted. The government printing office supplies the jacket covers.

3.6 Processing and Reviewing Policies:

Policies Regarding the Processing of Drug Master Files

- Upon receipt, an original DMF submission will be examined to see if it satisfies the minimum format and content requirements. FDA will give the submission a DMF number and acknowledge its receipt if it is administratively acceptable.
- A letter of explanation from the Drug Master File Staff will accompany the submission if it is administratively incomplete or inadequate, and no DMF number will be assigned to it.

4 DRUG MASTER FILE REVIEW

- There is never approval or disapproval for a DMF.
- When a DMF is received, its administrative content is examined. This may take two to three weeks.
- An Acknowledgement Letter will be sent to the holder of the DMF number informing them that the DMF is acceptable from an administrative standpoint if the DMF is accepted.
- A letter is sent to the DMF holder if FDA reviewers discover inaccuracies in the information provided in the DMF. At the same time, the FDA will let the person who relies on the information in the inadequate DMF know that the supporting DMF needs more information.
- The deficiency's general subject is identified, but only the DMF holder is informed of its specifics. In addition to providing the requested information to the DMF in response to the agency's deficiency letter, the holder ought to send a copy of the transmittal letter to the affected individuals who rely on the DMF as well as to the FDA reviewing division that discovered the deficiencies. The transmittal letter will let people know that the problems have been fixed.

4.1 Holder Obligations:

Any addition or change, including a change to a customer's authorization, should be submitted twice and adequately cross-referenced to

previous submissions. The reference ought to incorporate date(s), volume(s), section(s) or potentially page number(s) impacted.

4.2 Notice Required for Changes to a DMF:

Any pertinent change to the DMF must be communicated by the holder to each affected applicant or sponsor who has referenced the DMF (21 CFR 314). 420 (c)). In order to permit the sponsor or applicant to supplement or amend any affected applications as required, notice should be given well in advance of the change.

4.3 Annual Update:

The holder ought to give a yearly report on the commemoration date of the first accommodation. Since the previous annual report on the DMF's subject matter, all modifications and additional information should be provided. If the DMF's subject matter has not changed, the holder should state that the DMF's subject matter is current.

4.4 Electronic Filing of DMF's and CTD:

- It is encouraged for businesses to submit their DMFs electronically, including updating their existing paper DMFs.
- All applications to CDER, including DMF's that are submitted in electronic organization Should be in ECTD design, except if a waiver is conceded. DMFs are eligible for waivers.
- The Common Technical Document (CTD) format is acceptable for paper DMFs but is not required. Requirement for electronic DMFs • Paper-only DMFs can be resubmitted as electronic DMFs. The entire DMF must be submitted again.
- There will be no need to submit any paper documents—including LOAs—after a DMF has been submitted electronically.
- Because it contains the necessary administrative information to identify the DMF, Module 1 is required for all eCTD submissions.
- Section 1.2 of Module 1 ought to contain the following data: Section 1.3 of the Cover Letter and Commitment Statement: Information about administration.
- Electronic DMFs can be signed with an electronic device.

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A COMPREHENSIVE REVIEW OF WOODFORDIA FRUTICOSA (L) KURZ: TRADITIONAL USES, PHYTOCHEMISTRY, AND PHARMACOLOGICAL ACTIVITIES

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Abstract - Since ancient times, traditional medicine has relied on *Woodfordia fruticosa (L.) kurz*, which belongs to the family Lythraceae, to treat common ailments. It is customarily utilized against various illnesses, including cold, toothache, blood contamination, disease, diarrhea, wounds, rheumatic agony, fever, urinary issues, irritation, antifertility and feminine issue. In vitro and in vivo models extensively validate the enormous potential and effects. In order to determine the bioactive components that contribute to the plant's therapeutic effect, the most recent information on Woodfordia fruticosa is absolutely necessary. Phytochemical testing reveals the presence of 61 compounds isolated from various plant parts, including glycosides, terpenes, flavonoids, tannins, sterols, phenolics, and essential oils. The plant has a wide range of pharmacological properties, including antihyperglycemic, antioxidant, anti-inflammatory, analgesic, hepatoprotective, antibacterial, gastroprotective, and wound healing properties, as demonstrated by pharmacological studies. The majority of the pharmacological activities of crude plant extracts have been reported. The activities of this plant's isolated compounds have only been the subject of a small number of studies. As a result, this review will contribute to the investigation of numerous distinctive pharmacognostic characteristics of the plant, as well as the therapeutic efficacy of the plant against a number of diseases. It will also recommend the need for additional investigations to investigate the plant's potential applications in practice.

Keywords: Phytochemistry, antioxidants, hepatoprotective and anticancer properties of Woodfordia fruticosa.

1 INTRODUCTION

Herbal medicines are made from various parts, like the leaves, stem, root, and flower, among others. of plants, which have been widely used to treat and cure a variety of diseases ever since ancient times. Because it is readily available on the market at a lower price, is regarded as having low toxicity, and is simple to prepare and use, even 80% of the population of developing countries rely on herbal medicine for their fundamental health requirements. The way the medicine is made, the part of the plant that is used, and how the patient should take it all have a major impact on how effective it is. Mainly because people believe that natural products are always safer, herbal medicines are frequently used to maintain health over time. Nevertheless, it was discovered that self-medication or over-the-counter administration may result in significant adverse effects or drug interactions. Consequently full information about home grown plants is additionally important for their safe use.

Woodfordia fruticosa (L.) kurz (W. fruticosa) is a Lythraceae herbal plant that is also known as Shiranjitea and Fire flame bush worldwide. This plant is primarily available in Asian countries at high altitudes in the south, with a few exceptions in Gulf countries and Africa. Acute diarrhea, hemorrhages, ulcerations, erysipelas, and wounds are all treated with it as a traditional method of medicine

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worldwide[4]. It has been observed that this plant's flower, which is in high demand on both the domestic and international markets in the Southeast Asian nations[5], is its most effective part. By examining the data provided by various journals on the use of this plant as ethnomedicinal or pharmacological uses in various systems of medicine, where the activities will be noticed based on various forms of extraction of plant and phytoconstituents responsible for treating a particular disease, this review will focus on the future aspect of this plant used for the development of potential lead compound.

2 BOTANY

W. fruticosa is a mature shrub or small tree that stands approximately 3.6 meters tall. The branches are for the most part lengthy and spread with scored stems. Subopposite or opposite leaf arrangements are used. The flowers, which typically bloom in May and June, are stunning red, numerous, cymose-structured, with additional panicles and glandular pedicles. The petals are barely straight and stretched out at the apex, slightly higher than the calyx teeth. The base of the calyx is campanulated, stripped, and covered in glandular dots. The numerous, shiny, small brown seeds have an obovate shape and a smooth surface. The young shoots are terete and white pubescent, and the bark is a distinct smooth cinnamon-earthy brown shaded with fibers coated. The fruits are small, ovate, membrane-covered, dehiscent capsules that split the calyx at the end.

3 DISTRIBUTION

It is found in a lot of southern Asian countries, as well as in some parts of Bhutan, China (Yunnan, Guangdong, and Guangxi), India, Myanmar (Burma), Nepal, Vietnam, Malaysia, Pakistan, Sri Lanka, and Gulf countries like South Arabia (SW-Saudi Arabia: Dhofar) and Oman (Asir). In addition, Java, Sumatra, Madagascar, Tanzania, and the Comores all offer.

4 TRADITIONAL USES

The flowers of this plant are used in the preparation of Aristha and Asava in the Ayurvedic medical system for both medicinal purposes and drug fermentation. Sunstroke patients received flower juice twice daily, and decoctions of bark juice and flower juice were used to treat colds. The plant was used to treat wounds in the western Ghat region of India. It was discovered that this plant was used to treat leucoderma disease by the Kondha tribe in Orissa. Indian ayurvedic pharmacopoeia says that the flower of W. fruticosa, which is called "Vrana," is used in an ointment to treat smallpox pimples. Leaf juice is used by tribal people in the Theni district of southern India to alleviate rheumatoid arthritis pain. This plant's flowers are regarded as astringent, pungent, cooling, and uterine narcotic, making them useful for toothache, blood infections, leprosy, dysentery, and fever. As a result, it has the same suppressive effect as Kapha and pitta in the Ayurvedic medical system. It is given to children with diarrhea along with honey. This plant's flower and leaf are used to treat a variety of ailments in Nepal, including fever, urinary problems, swelling, and menstrual issues, among others.

5 PHYTOCHEMISTRY

The phytochemicals present in the plant consist of both organic and inorganic chemicals, which are secondary metabolites of the plant. These chemicals have various activities which indirectly lead to the pharmacological response of the plant. The plant contains various tannins, flavonoids, alkaloids, glycosides, sterols and triterpenoids. The leaves of the *W. fruticosa* were observed to have polyphenolic groups such as lawsone, glucogallin, ellagic acid, gallic acid, quercetin 3-O-(6- β-galloyl)-β-d-galactopyranoside, quercetin 3-O-α- L-

arabinopyranoside, methyl 3-O-methylgallate, myricetin 3-O-α-L arabinopyranoside, etc and essential oil containing α-pinene, β-selinene, γ-curcumene, germacrene-D, β-caryophyllene, etc.

6 PHARMACOLOGICAL ACTIVITIES

6.1 Anti-hyperglycemic Activity:

A metabolic disorder is the cause of hyperglycemia, a condition in which the blood glucose level rises due to a variety of factors such as insulin resistance, pancreatic damage, and so on. Antihyperglycemic drugs are those that lower blood glucose levels to a normal range[34]. When Tayab et al. looked at the -amylase inhibitory activity, they found that the n-hexane Fraction of the Methanolic Extract of W. fruticosa Leaves (NHFMEW) had a significantly lower IC50 value than acarbose. For NHFMEW and Acarbose, the IC50 values were 103.771.02 g/ml and 156.321.32 g/ml, respectively. This suggests that the antihyperglycemic activity of the plant extract can be attributed to a bioactive component. Streptozotocin-nicotinamide was used in another study to induce diabetes in rats, who were then given methanolic extracts of W. fruticosa at doses of 100, 200, and 400 mg/kg body weight. Extract was found to aid in the recovery of the pancreatic beta cell and to alter the expression of the Glucose Transporter (GLUT) proteins GLUT-2 and GLUT-4, which help regulate normal blood glucose levels by translocating insulin. W. fruticosa flower extract was given to normal mice and alloxan-induced diabetic mice orally in various doses, either with or without glyburide, in another study.

6.2 Anti-depressant Activity:

Depression is a mental health condition characterized by a persistently low mood or a loss of interest in activities, which significantly limits one's ability to carry out day-to-day activities. A review was performed to assess the stimulant action of NHFMEW and Ethyl Acetic acid derivation Part of the Methanolic Concentrate of W. fruticosa leaves (EAFMEW) utilizing creature models, in particular Tail Suspension Test (TST) and Constrained Swimming Test (FST). The findings showed that in both models, mice treated with NHFMEWF or EAFMEWF at doses of 100 mg/kg or 200 mg/kg body weight exhibited active behaviors like swimming and struggling by reducing immobility behaviors. EAFMEWF had a significant antidepressant-like effect at 200 mg/kg in both models, reducing the duration of the depression-like state (immobile behavior) by more than 50% (compared to the control group) and being comparable to the positive control group (fluoxetine-treated).

6.3 Anti-inflammatory Activity:

The multi-step process of harmful substances like microbes (bacteria, viruses, and so on) entering the body causes inflammation. or wounds that hurt, swell, heat, and turn red. In the model of histamine, carrageenan, dextran, formaldehyde, and serotonin-induced rat paw oedema, the methanolic extract of W. fruticosa flowers exhibits effective anti-inflammatory activity at doses of 400 mg/kg and 600 mg/kg body weight, respectively. Methanolic flower extract significantly (p 0.05) reduced the volume of paw oedema in all models, according to the experiment.

6.4 Anti-cancer Activity:

In the PLC/PRF/5 human liver cell line, it was demonstrated that ethanolic extract of W. fruticosa flowers has anticancer properties. The effect of the extract was evaluated using serum parameters, liver histopathology, and immunohistochemical analysis of vascular endothelial growth factors. The MTT assay was used to determine cell viability in this analysis. The analysis suggests that the extract's potential chemopreventive property may be due to the synergistic effect of the

phytomolecules it contains. W. fruticosa flowers could potentially be used to prevent hepatic cancer on the basis of this study.

6.5 Efficacy Against Bacteria:

The antibacterial movement of a compound is the capacity to obliterate or repress the development of microbes without displaying harmfulness to the encompassing cells. In the agar well diffusion method, the standard antibiotics ciprofloxacin and amoxicillin were used to test the methanolic extract of W. fruticosa flowers against gram-positive bacteria (Bacillus subtilis and Micrococcus flavus) and gram-negative bacteria (Pseudomonas pseudoalcaligenes) at two different doses. The methanolic extract was found to be more effective against gram-negative bacteria than it was against gram-positive bacteria.

6.6 Activity Against Oxidants:

Oxidative stress, which damages the various cells, DNA, proteins, or lipids of the human body and contributes to diseases such as diabetes, heart disease, and cancer, among others, is caused by the disproportion between the cellular uptakes of reactive oxygen species (ROS) and cellular production. Antioxidants can stop oxidative stress from causing necrosis or apoptosis in cells. Chaturvedi et al. extracted the bark, flowers, and leaves of the W. fruticosa plant using ethanol, distilled water, and methanol.

6.7 Activity Against Enteroviruses:

The positive, small single-stranded RNA virus Enterovirus 71 (EV71) is a member of the Picornaviridae family and is a member of the Enterovirus genus. It causes severe hand, mouth, and foot infections in infants and children. It is known that compounds that are effective against enteroviruses also have anti-enteroviral properties. The anti-enteroviral activity of an extract of W. fruticosa flowers and an isolated gallic acid was examined, as reported by Choi et al. When compared to the flower extract of W. fruticosa, the gallic acid that was isolated from the extract is more effective against EV.

6.8 Prebiotic Function:

Two lactic acid bacteria with prebiotic-like characteristics, Lacticaseibacillus casei and Lacticaseibacillus rhamnosus, were used to test the effect of W. fruticosa extract. Probiotic growth was stimulated at 0.5 and 1 mg/ml of W. fruticosa (p 0.05), adhesion to Caco2 cells was improved (p 0.05), and foodborne pathogens such as Escherichia coli and Staphylococcus aureus were prevented (p 0.05). Variation in the metabolite pool as a result of W. fruticosa supplementation was attributed by the comprehensive metabolomic studies. Therefore, W. fruticosa, which has the potential to be a prebiotic, can be utilized in the creation of novel health-enhancing products focusing on the regulation of gut microbials.

7 CONCLUSION AND FUTURE PERSPECTIVE

Because the conventional medical system makes use of synthetic compounds that can have one or more negative effects, scientists are constantly researching natural products. W. fruticosa is an effective traditional medicine that has been used to treat a wide range of conditions since ancient times. The current survey revealed the information connected with customary purposes, phytochemical constituents, and pharmacological exercises of W. fruticosa. The data that were reported indicate that the majority of the research was carried out using extracts of various plant parts, particularly the flowers, which demonstrated a diverse range of pharmacological activities. The various pharmacological activities of W. fruticosa are depicted graphically. However, their specific pharmacological effects necessitate an understanding of the molecular mechanism. Over 60 substances that have been isolated or

identified from various W. fruticosa parts are discussed in this article. The majority of chemical components belong to tannins, flavonoids, alkaloids, glycosides, sterols, and triterpenoids, according to phytochemical research. Only a small number of these identified phytochemicals have significant pharmacological effects. Although W. fruticosa extracts have been the subject of a great deal of study, isolated phytochemicals, which may have a significant impact on drug development, have not yet been investigated.

In the future, bioassay-guided isolation may be used to identify the most important bioactive chemicals that cause pharmacological effects. Even though W. fruticosa is used in a lot of traditional and traditional medicines, little is known about the exact mechanisms behind its pharmacological effects. To develop safe and effective herbal medicines for better disease management, extensive research on the various phytochemicals derived from this plant is required to identify their precise target sites, structure-activity relationships, pharmacological activities, and mechanism of action.

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A CRITIQUE OF THE ANALYSIS OF QUALITY CONTROL FOR TABLETS IN ORAL DOSAGE FORMS

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Abstract - Tablets are the most widely used oral dosage form because they are simple to take by patients and rely on by many. The appropriate medication for patients to take is prescribed by pharmacists; this is based on the brand, product quality, and market availability. In order to meet the criteria in advance, the quality tests are carried out this way. Analyzing each step on a regular basis to ensure high product quality is quality control. There are numerous brands and dosage forms on the market. Techniques and methods for evaluating tablets have been discussed in this review article, and they are applicable to the production of all dosage forms.

Keywords: Disintegration, Evaluation of Tablets, Excipients, Dissolution, Pharmacopoeia, Active Pharmaceutical Ingredient API, Disintegration, Dosage Form, Capsules, Quality Control.

1 INTRODUCTION

Pharmaceutical and dietary supplement dosage forms are manufactured under regulated terms and laws into tablets and capsules. During the manufacturing process, regulations are imposed to guarantee the tablets and capsules' quality, effectiveness, and safety. In order to meet market regulations and standards, the products undergo numerous quality tests to test these qualities.

Both the tablets and the capsules are subjected to biological, chemical, and physical tests as part of the testing procedures. These are carried out in accordance with the applicable nations' pharmacopoeia using standard quality control procedures. In order to meet the global market's required regulated standards, many nations adhere to the British Pharmacopoeia. In every industry, the primary stages of pharmaceutical products are manufacturing, production, packaging, and testing.

2 TABLETS

Tablets, which hold the most significant and significant position among all pharmaceutical formulations, are the most typical oral route of administration. In the pharmaceutical markets, oral dosage forms hold a greater position of importance. They are manufacturers of pharmaceuticals in both large and small units. In the process of packaging tablets, the size, shape, and thickness of the tablets are more important than their organoleptic properties, which include their color and smell.

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Different pharmacopeia quality control trial of tablets:

The British Pharmacopoeia says that tablets are tested for one active ingredient; 2 Destruction; 3 Content consistency; four Labeling

The API determines the variety of tablet types. The various types include:

- Uncoated Tablets
- Bubbly tablets
- Covered tablets
- Gastro Safe Tablet
- Adjusted Delivery Tablet
- Dispersible Tablet
- Intestinal Covered tablet
- Solvent Tablet
- Controlled discharge tablets
- Supported discharge tablets

The quality control trial of these tablets rely upon the idea of the tablet. The tablets that are broken, damaged, or unblinded to the ingredient are taken out during the quality control tests.

Hardness: It is the force necessary to break the tablet when it is pushed to the edge. The test is done to see if the tableting machine needs to adjust the pressure. The disintegration test is influenced by hardness. If the tablet is too hard, it might not break down in the time needed. Additionally, the tablet will not be able to withstand handling during subsequent processing, such as packaging or coating, if it is too soft. Before rejecting a batch, we first check the tablet's disintegration if its hardness is too high. We accept the batch if the disintegration is within the limit.

Appearance in General: Consumer acceptance, lot-to-lot uniformity control, and tablet-to-tablet uniformity all depend on a tablet's overall appearance, identity, and elegance. The measurement of things like size, shape, color, and whether or not they smell, taste, or both are part of the control of the general appearance. Tablets may differ in size and shape.

Unique marking for identification: Printing, engraving, or embossing are all ways to use these. These can be any symbols associated with the dosage form or the company identification marks.

Friability: The tablets' friability is assessed using the Roche Friabillator. Before placing the tablets in the device, their initial weight is checked, and batches are separated for this purpose. The tablet's initial and final weights are checked. It is acceptable to compress tablets that lose less than 0.5 to 1.0 percent of their original weight. Hardness testing is frequently associated with brittleness.

Test of thickness: Because it is not an official test, the thickness test is only done on a small number of tablets. The tablet's thickness is determined using a screw gauge and Vernier caliper.

Test of weight variation: It is done to make sure the tablet is uniform.

Test for dissolution: A legal test is dissolution. The dosage forms are dissected to check the percentage of release.

Evaluation tests are performed on the tablets before they are processed to determine the best granule testing method for compressing them.

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The API formulations that are compressed into tablets are known as granules. Combining the API, excipients, and binders creates granules. This dough is used to make dried granules that are then tested for evaluation.

1. Size and shape of particles can be determined: The size and shape are determined by the requirements of the processing and during granulation. The shape can be found in the following ways: Microscopy, light screening, sedimentation rate, and sieving
2. Granule surface area: Most of the time, this is used for drugs, but not for granules.
3. Density: Tablet density is its compressibility, porosity, and ability to dissolve. Density is measured using: The equation shown in Figure 1 can be used to determine the granular density.

Density D=M/Vp –Vi

Vp- total Pressure; Vi- Volume of intrusion

Figure 1 Bulk density apparatus.

Friability and strength of the granules: to ascertain the shifts in compressibility and granulation size distribution.

Flow attributes: For tablet uniformity, this is to determine the granule flow from the hopper to the die cavity. Three parameters determine granules' flow properties:
Position of repose: both the static and dynamic repose angles.

Hausner's proportion: to anticipate the property of powder flow.
The Hausner's ratio is the bulk density divided by the tapped density. It refers to the amount of water in the granules.

% moisture content = initial weight divided by final weight divided by initial weight multiplied by 100

3 DISCUSSION

- The API, biological types, and type of tablet are used to evaluate the tablets.
- Uncoated Tablets include, among others, 400 mg of aspirin, 500 mg of paracetamol, 250 mg of acetazolamide, 10 mg of cetirizine, 50 mg of atenolol, and 50 mg of amlodipine intravenously.
- Ranitidine, co-codamol, sodium dichloroisocynuarate, ascorbic acid, and other effervescent tablets are among them.

- Coated tablets include, among others, enteric coated Diclofenac and Aspirin.
- On the pharmaceutical market, numerous tablets with standard procedure and API content are marketed under a variety of brand names.

4 CONCLUSION

Depending on whether the company operates on a large or small scale, the testing for quality control is assigned to production or quality control. Before putting the tablets on the market, Quality executives evaluate their quality tests. The FDA and RA bodies regularly examine these. As previously mentioned, the quality tests reveal errors, counterfeit goods, and low-quality products. This analysis and the outcomes of the tests, which achieve therapeutic and quality objectives, serve as the foundation for the products' standards. Pharmaceutical companies are obligated to produce dosage forms that are resistant to shaking and handling in order to increase demand and shelf life in the pharmaceutical markets.

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PREPARATION AND ASSESSMENT OF A SOFT GEL FORMULATION MADE WITH GELLAN GUM AND CONTAINING PARACETAMOL

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Abstract- Using sodium citrate as a cation source and gellan gum as a gelling agent, this study set out to create a soft paracetamol gel. Each batch had two different sodium citrate concentrations (0.3 and 0.5 percent) and three different concentrations of gellan gum (0.1, 0.3, and 0.5 percent). The consistency of the paracetamol gel was reliant upon the grouping of gellan gum, sodium citrate and co-solute. Paracetamol was released completely in 30 minutes in the dissolution study of a soft gel containing 0.3% gellan gum and 0.3% sodium citrate. Paracetamol was soluble when polyethylene glycol 400 was used as a solubilizer. When tested by human volunteers, each gel had acceptable sensory properties. The developed and optimized formulation's performance characteristics did not significantly change during the four-week short-term stability study at various temperatures.

Keywords: Melt-in-mouth gel, soft gellan gum, gellan gum, paracetamol, dissolution study.

1 INTRODUCTION

Polymers with at least two components aggregate to form gels; the fluid component and the gelling agent. Gellan gum, carrageenan, gelatin, sodium alginate and gelatin are broadly utilized gelling specialists in drug businesses. Gellan gum was chosen as a gelling specialist in the current examination to plan simple to swallow oral sedated prepared to utilize delicate gel. Sphingomonas elodea fermentation yields gellan gum, a water-soluble linear anionic polysaccharide of high molecular weight. Acetate and glycerate are the two acyl substituents found in the native form of gellan gum. Under ideal conditions for gelling, deacylated gellan gum produces hard, non-elastic, and brittle gels, whereas acylated gellan gum produces soft, very elastic, and non-brittle gels. Deacylated gellan gum forms brittle gels with a weak gel network and crumbles in the mouth to cleverly mimic the "melt in mouth" sensation with the release of flavors and water, which facilitates the straightforward release of water-soluble drugs from gel dosage forms. Gellan gum has free carboxylate groups in its structure; Since gellan gum is anionic, it would undergo ionic gelation in the presence of acidic cations like K+, Na+, Ca++, and Mg++. The formation of double helical junction zones from random coil chains (coil-to-helix transition), followed by the aggregation of double helical segments to form a three-dimensional network through complexation with cations and hydrogen bonding with water, is the

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mechanism by which gelation occurs. The pH of the solution has an effect on the behavior of aggregates. Gels of varying gel strength and gel texture can be produced by varying the concentration of gellan gum and cation.

The development of a hydrophilic gel dosage form for the oral administration of paracetamol was the goal of this study. Patients with dysphagia, geriatric patients, and children can take this gel dosage form. Without water, the gel dosage form is easy to swallow. Because the gels are soft and smooth, the patient will not feel any pressure in their throat. In terms of patient acceptance and attractive appearance, the gel dosage form surpasses the liquid dosage form. As oral medicated gels will be packed in unit doses, the issue of patients measuring doses is outweighed. The gel dosage form may be versatile in that it can be taken alone or in combination with food items like breads and biscuits.

As a model, paracetamol, a BCS (biopharmaceutical classification system) class III analgesic and antipyretic, was chosen. Since paracetamol has a bitter taste, one of the goals of developing the paracetamol soft gel is to mask that taste.

The dry gellan gum powder Kelcogel® was generously provided by CP Kelco (USA). Green Pharmaceuticals (India) donated the patent for Paracetamol. Polyethylene glycol 400 (Stake 400) and citrus extract was acquired from Laser Research centers (India). Apex Pharmaceuticals (India) supplied methylparaben and propylparaben. Lincoln Pharmaceuticals Ltd. (India) generously provided the sucralose and sodium citrate. The local market provided the food-grade sucrose.

A magnetic stirrer (Remi Magnetic Stirrer 2MLH, Mumbai, India) was used to stir the dry gellan gum powder into 50 milliliters of distilled water at 95 degrees for 20 minutes to aid in the hydration of the gellan gum. Paracetamol, PEG 400, citric acid, and preservatives (methylparaben, propyleparaben) were added to the gellan gum solution while continuously stirring. The required quantities of co-solutes (sucrose and sucralose) were added to the gellan gum solution. Finally, 10 milliliters of distilled water containing the required amount of sodium citrate were added to the mixture. Throughout the manufacturing process, the gel's weight was continuously monitored until it reached 100 grams using distilled water. A polyethylene bag with an airtight seal contained the gellan gum, paracetamol, and other additives mixture. The combination was permitted to cool to room temperature (25±5o) to shape gel. The gels were made with two different sodium citrate concentrations (0.3 and 0.5 percent) and three different concentrations of gellan gum (0.1, 0.3, and 0.5 percent). Table 1 displays the composition of paracetamol soft gel (batches PG1-PG6).

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Table 1 Formulation of paracetamol soft gel

Ingredients	Batch Code					
	PG1	PG2	PG3	PG4	PG5	PG6
Paracetamol %	2.5	2.5	2.5	2.5	2.5	2.5
Gellan gum %	0.1	0.1	0.3	0.3	0.5	0.5
PEG 400%	10	10	10	10	10	10
Citric acid %	0.05	0.05	0.05	0.05	0.05	0.05
Sucrose %	66	66	66	66	66	66
Sucralose %	0.3	0.3	0.3	0.3	0.3	0.3
Sodium citrate %	0.3	0.5	0.3	0.5	0.3	0.5
Methylparaben (mg)	0.18	0.18	0.18	0.18	0.18	0.18
Propylparaben (mg)	0.02	0.02	0.02	0.02	0.02	0.02
Raspberry flavor %	2	2	2	2	2	2
Water %, up to	100	100	100	100	100	100

The clarity, texture, and consistency of the paracetamol soft gels were looked at. In addition, the viscosity, pH, drug content, and in vitro drug release of paracetamol soft gels were examined.

After lightly rubbing the gel sample between two fingers, the texture of the soft gel was evaluated in terms of stickiness and grittiness. The viscometer Brookfield DV-II+Pro was used to measure the viscosity of batches PG1 through PG6. By making a uniformly sized cut in the polyethylene plastic bag, the paracetamol soft gel was squeezed out, and the viscosity was measured using spindle number LV4 at a rotation speed of 50 RPM at 25°. Each time, fresh samples were used to measure the viscosity. Table 2 displays the results of the soft gel's viscosity measurement (batches PG1-PG6). Table 2 displays the pH of the paracetamol soft gels, which were measured using an Electroquip Digital pH meter at 25°C. By eluting the drug from 10 grams of the gel in phosphate buffer pH 5.8, the drug content of the paracetamol gel was estimated. After filtering the sample through 0.45 filters, a spectrophotometric measurement at 243 nm was used to estimate the drug content.

Table 2: Evaluation of paracetamol soft gel

Parameters	Batch Code (n=3)					
	PG1	PG2	PG3	PG4	PG5	PG6
Viscosity (cPs)	1872±35	2564±52	6575±80	7570±91	10162±107	12182±135
pH	5.93±0.05	6.08±0.08	6.01±0.04	6.12±0.09	5.94±0.05	6.10±0.06

The ready-to-use soft gel (10 g) containing 250 mg of paracetamol was used in the dissolution test, which was performed using the USP test dissolution apparatus II with a paddle at a speed of 100 RPM and 900 ml of pH 5.8 phosphate buffer at 37°C. After being sufficiently diluted, five milliliter samples were taken at various intervals and analyzed spectrophotometrically at 243 nm with a Shimadzu-1700 UV/Vis spectrophotometer. After each withdrawal, the new dissolution medium was replaced.

The taste of paracetamol soft gel (PG3) was evaluated by ten healthy adult volunteers. Every volunteer

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received a 10 g dose of the paracetamol soft gel, which contained 250 mg of the medication. They were instructed to swallow the gel for 5 seconds. It was instructed to the volunteers not to swallow the gel. The volunteers were asked to wait 0.5 hours between tastings of the two samples. The gel's bitterness, aftertaste, sweetness, and flavor were all topics for the volunteers to discuss. Additionally, the grittiness of the mouth was examined. From non-bitter (NB), to less bitter (LB), to bitter (BT), to very bitter (VB), bitterness and aftertaste were rated. From less sweet (LS), sweet (SW), and very sweet (VS), sweetness was rated. The flavors ranged from mild (LS) to moderate (MD) to excellent (GD). From less (TL), to moderate (TT), to good (TS), mouth feel was evaluated. the evaluation of paracetamol soft gel's flavor.

The evaluation of the batch PG3 paracetamol gel's flavor. Every one of the ten workers saw the delicate gel as non-unpleasant. The gelling agents may reduce bitter substances' diffusion from the gel to the taste buds, which is one possible explanation. The volunteers, on the other hand, reported a slight bitter aftertaste. Expansion of flavors and sugars is the preeminent and least complex methodology for taste veiling particularly on account of pediatric plans. This provides a taste-masked gelled pharmaceutical composition for the administration of a relatively large number of medicines with unpleasant tastes. In order to cover up the taste of paracetamol, sugar was chosen as a sweetener for soft gel. Because sugar molecules may have been entangled in the gellan gum gel network, sucrose (66.6%) was unable to completely mask the bitter taste. Non-carcinogenic and 300-1000 times sweeter than sucrose, sucrose was chosen as an auxiliary sweetener. The flavor raspberry was chosen because, to some extent, it helps to cover up the drug's bitter taste.

It is accounted for that low acylated gellan gum gives nonelastic and weak gel with an exceptionally low fixation, for example, 0.05%. Be that as it may, the expansion of co-solute above 60% outcomes in the development of adaptable and less amassed gellan gum gel network because of concealment of total of gellan chains and cause decrease in weakness of low acylated gellan gum gels. In the current review, high grouping of sucrose was utilized and subsequently high convergences of gellan gum (0.3 and 0.5%) were utilized. Sworn and co., reported that the concentration of co-solute would decrease the amount of cations needed for gellan gum to gel. This could be one reason why a soft gel with 0.3% gellan gum and 0.3% sodium citrate has the best consistency.

One of the major issues with low-acylated gellan gum gels is syneresis. Mashimo and other, reported that free water exists even in the gel phase of gellan gum. At room temperature (25°C), syneresis was not observed, probably because co-solute bound free water. The formulations' pH, viscosity, and appearance were not significantly altered in the stability studies, as shown in Table 4. There was no evidence of paracetamol precipitation in any of the soft gels. In the samples that were kept at 45°C, there was a slight syneresis.

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THE EFFERVESCENT METHOD CAN BE USED TO PRODUCE FAST-DISSOLVING TABLETS OF FEXOFENADINE HCL

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Abstract - In this study, an effervescent method was used to make fast-dissolving fexofenadine HCl tablets with the intention of increasing patient compliance. There are three super-disintegrants: To improve mouthfeel, crospovidone, croscarmellose sodium, and sodium starch glycolate were combined with directly compressible mannitol (Pearlitol SD 200) in various ratios, as well as sodium bicarbonate and anhydrous citric acid. The tablets' hardness, friability, uniformity of drug content, and in vitro dispersion time were all tested on the prepared batches. Three formulations were tested for drug-excipient interaction (IR spectroscopy), in vitro drug release pattern in pH 6.8 phosphate buffer for three months, and the in vitro dispersion time (approximately 20 s). Based on the in vitro drug release characteristics compared to conventional commercial tablet formulation (t50% 15 min), the formulation ECP3 with 8% w/w of crospovidone and mixture of 24% w/w sodium bicarbonate and 18% w/w anhydrous citric acid emerged as the best among the three promising formulations (t50% 4 min). In vitro dispersion time and drug content did not change significantly (P 0.05) during short-term stability tests on the formulations.

Keywords: Fast-dissolving tablets containing fexofenadine HCl, crospovidone, croscarmellose sodium, and sodium starch glycolate in an effervescent form.

1 INTRODUCTION

Despite significant advancements in drug delivery, the oral route continues to be the best method for administering therapeutic agents due to its low cost and ease of administration, which results in high patient compliance. Drug delivery systems that are safer and more advanced have been developed as a result of research focused on patient convenience and compliance. Due to their rapid disintegration or dissolution, self-administration (even without water or chewing), and increased consumer choice, fast dissolving drug delivery systems have recently begun to gain popularity and acceptance. Patients who have difficulty swallowing tablets or capsules now have viable dosage alternatives thanks to recent technological advancements.

Because it is difficult for many patients to swallow tablets and hard gelatin capsules, they do not follow prescriptions, which leads to a high rate of non-compliance and ineffective treatment. By developing a convenient dosage form for administration and improving patient compliance, recent advancements in novel drug delivery systems (NDDS) aim to improve drug molecule safety and efficacy; one such methodology is quick dissolving

tablets. Fexofenadine HCl (FXD) is an antihistamine that does not cause sedation and is used to treat allergic conditions like urticaria and seasonal allergic rhinitis. A suitable and practical strategy for achieving the desired objective of faster dissolution and dissolution characteristics with increased bioavailability is the idea of formulating fast dissolving tablets containing fexofenadine HCl.

FXD came as a free sample from India's Aurobindo Pharmaceuticals, based in Hyderabad. Samples of crospovidone (CP), croscarmellose sodium (CCS), and sodium starch glycolate (SSG) were presented by the Wockhardt Research Centre in Aurangabad, India. Strides Acrolabs, Bangalore, India, generously donated directly compressible mannitol (Pearlitol SD 200) and sodium stearyl fumarate (SSF). The wide range of various synthetic compounds utilized were of insightful reagent grade.

The effervescent method was used to make tablets that dissolve quickly. The sodium bicarbonate and anhydrous citric acid were thoroughly mixed in a mortar to obtain a uniform powder before being added to the other ingredients. All of the ingredients, with the exception of SSF and purified talc, were accurately weighed and sifted through #44 mesh separately. After being filtered through sieve No. 44 ingredients were thoroughly blended in a tumbler-shaped blender made in our laboratory. Using 8 mm round flat punches, the mixture was directly compressed into 150 mg tablets on a 10-station rotary machine (Clit, Ahmedabad, India). The formulas in Table 1 were used to prepare the tablets.

Table 1 Composition of different batches of fast dissolving tablets of fexofenadine hydrochloride

Ingredients* (mg)	Formulation Code#									
	EC_0	ECP_1	ECP_2	ECP_3	$ECCS_1$	$ECCS_2$	$ECCS_3$	$ESSG_1$	$ESSG_2$	$ESSG_3$
Fexofenadine HCl	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00
Sodium bicarbonate (8-24%)	24.00	12.00	24.00	36.00	12.00	24.00	36.00	12.00	24.00	36.00
Citric acid (6-18%)	18.00	9.00	18.00	27.00	9.00	18.00	27.00	9.00	18.00	27.00
Crospovidone	--	3.00	6.00	12.00	--	--	--	--	--	--
Croscarmellose sodium	--	--	--	--	3.00	6.00	12.00	--	--	--
Sodium starch glycolate	--	--	--	--	--	--	--	3.00	6.00	12.00
Aspartame	7.50	7.50	7.50	7.50	7.50	7.50	7.50	7.50	7.50	7.50
Flavour	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Sodium stearyl fumarate	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Talc	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Pearlitol SD 200	64.5	82.50	58.50	31.50	82.50	58.50	31.50	82.50	58.50	31.50
Total weight	150.0	150.0	150.0	150.0	150.0	150.0	150.0	150.0	150.0	150.0

*Quantity expressed is in mg/tablet. #A batch of 60 tablets was prepared for each formulation

Individually, twenty tablets were selected at random and weighed. To determine the variation in weight, the individual weights were compared to the average weight. The tablets' hardness and friability were measured, respectively, with a Monsanto hardness tester and a Roche friabilator. Ten tablets were weighed and powdered in order to determine the consistency of the contents. Methanol was used to extract the 30 mg of FXD powder, and the resulting liquid was filtered

(Whatman No. 1 filter cloth). After a suitable dilution with methanol, the absorbance at 259 nm was used to measure the FXD content in the filtrate. The standard calibration curve was used to ascertain the amount of drug. The mean percent drug content was determined as a normal of three determinations. One tablet was placed in a beaker containing 10 milliliters of pH 6.8 phosphate buffer at 37 0.5 degrees Fahrenheit to determine the in vitro dispersion time. In order to rule out drug-carrier interactions, IR spectra of FXD and its formulations were obtained using the potassium bromide pellet method and a Perkin-Elmer FTIR series (Model 1615) spectrophotometer.

In a USP XXIII type-2 dissolution apparatus (Electrolab, Model-TDT 06N) with a paddle stirrer at 50 rpm and 900 ml of pH 6.8 phosphate buffer at 37 0.5 o as the dissolution medium, in vitro dissolution of FXD fast dissolving tablets was investigated. In each test, a single tablet was used. By measuring the absorbance at 259 nm, aliquots of dissolution medium (5 ml) were taken out at specific times and analyzed for drug content. At each time point, a new volume of dissolution medium was added to the volume that had been taken out. The percentage of FXD released over time was calculated and plotted.

According to ICH guidelines, short-term stability studies on the promising formulations (ECP3, ECCS3, and ESSG3) were conducted by storing the tablets in an amber-colored glass vial with a rubber stopper at 40o/75% RH for three months. The tablets were visually examined for any physical changes, changes in drug content, and changes in the in vitro dispersion time at intervals of one month.

The effervescent method was used to make FXD's fast-dissolving tablets because it has the advantage of covering up taste. Additionally, the formulations included mixtures of sodium bicarbonate and anhydrous citric acid in varying ratios as super-disintegrants, as well as aspartame 5% and 1% flavor, to improve mouthfeel. Straightforwardly compressible mannitol (Pearlitol SD 200) was utilized as a diluent to upgrade mouth feel. Nine formulations were created, along with a control formulation EC0 (without super-disintegrant). Due to uniform die fill and free flowing blends (angle of repose less than 30 degrees, Carr's index less than 15%), the tablets that were produced had a weight that was consistent with IP specifications and had an acceptable variation of less than 7.5%. The drug content was found to be within acceptable limits, between 95 and 101 percent. The tablets were found to have a hardness of 2.5 to 2.8 kg/cm2. The tablets had a good mechanical resistance because their friability was below 1%. There were three formulations designed out of all of them: ECP3, ECCS3 and ESSG3 were viewed as promising and shown an in vitro scattering time going from 19 to 26 s, which works with their quicker scattering in the mouth.

Overall, the formulation ECP3, which contains 8% w/w of crospovidone and a mixture of 24% w/w sodium bicarbonate and 18% w/w anhydrous citric acid, was found to be promising. In comparison to the control formulation (EC0), which has an in vitro dispersion time of 498 s,

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ECP3 has an in vitro dispersion time of 20 s.

In a pH 6.8 phosphate buffer, in vitro dissolution studies were carried out on the promising formulations (ECP3, ECCS3, and ESSG3), the control (EC0), and commercial conventional formulations (CCF). The various dissolution parameter values, namely, Dissolution efficiency at 10 minutes (DE10 min)[11], t50%, t70%, and t90%, as shown in the dissolution profiles in fig., percent drug dissolved in 5 minutes, 10 minutes, and 15 minutes (D5, D10, and D15). 1. According to these data, the formulation ECP3 released five times as much drug in 10 minutes as the control formulation and nearly four times faster drug release (t50% 4 min) than the commercial conventional tablet formulations of FXD (t50% 15 min).

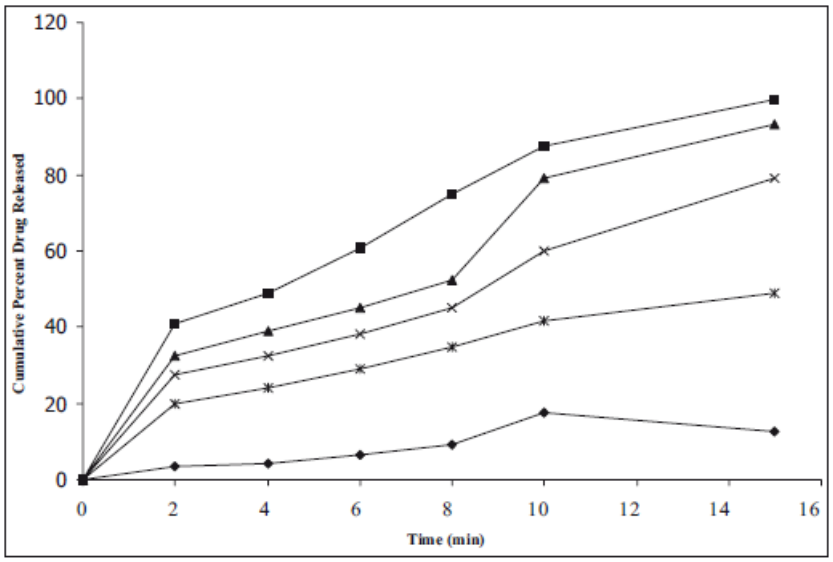

Fig. 1 Cumulative percent drug release versus time profile of promising formulations.

All of the excipients are compatible with the drug, according to IR spectroscopic studies. All of the typical peaks of FXD pure drug were visible in the IR spectrum of ECP3, indicating that the drug did not interact with the formulation's components. At the end of the three-month period, the above formulations' short-term stability studies revealed no significant changes in the drug content or in vitro dispersion time (P 0.05).

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EXPLORING ORAL MUCOSAL DRUG DELIVERY SYSTEMS: A COMPREHENSIVE REVIEW

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Abstract - Despite significant advancements in drug delivery, the oral route remains the most important method for systemic drug administration. For self-medication, the parenteral route is rarely utilized. It has been known for a really long time that buccal and sublingual organization of medication solute is quickly ingested into the reticulated vein, which lies under the oral mucosa. The oral mucosa is relatively permeable and has a lot of blood supply. The buccal mucosa is four to one thousand times more permeable than skin. The buccal route has several advantages over the oral route, including QWICK ACTION, avoiding first-pass metabolism, the drug not being exposed to stomach acid, and improved patient compliance, particularly in pediatric and geriatric patients. It is the goal of this article to survey the oral mucosal medication conveyance by talking about momentarily the underlying element of mucosa as medication conveyance, for example, buccoadheshive film and tablet, sedated bite gum, quick dissolving tablet, film and container and so on.
Keywords: Sublingual buccoadhesive, drug administration, patient compliance, pediatric.

1 INTRODUCTION

To achieve a systemic pharmacological effect, a drug can be administered in a variety of ways. The most widely recognized technique for drug organization is by means of per oral course in which the medication is gulped and enters the foundational dissemination fundamentally through the film of the small digestive tract. The most crucial method of drug administration for systemic effect is oral administration. Self-medication is not typically administered via parenteral route.

It is likely that oral administration accounts for at least 90% of all drugs used to produce systemic effects. After being taken orally, drugs may be absorbed at a variety of body locations between the mouth and the rectum. In most cases, it is desirable for a drug to have a faster rate of action the higher up along the alimentary tract it is absorbed. When taken orally, a drug must withstand significant pH changes as it moves through the gastrointestinal tract, as well as the assault of enzymes that break down food and the metabolism of the microflora that live there.

It is estimated that 25% of people have difficulty swallowing tablets and capsules, so they do not take their medications as prescribed by their doctors, leading to a high rate of non-compliance and ineffective treatment. Patients of all ages, including infants, geriatrics, bedridden patients, active working patients who are busy or traveling, and those who do not have access to water, all experience difficulty. In these instances, oral mucosal drug delivery is the method of choice.

It has been known for centuries that drug solutes administered sublingually and buccally are swiftly absorbed into the reticulated vein, which is beneath the oral mucosa. They then travel through the facial veins, internal juglar vein, and braciocephalic vein before draining into the systemic circulation. As a result, the hepatic first-pass elimination of drugs can be avoided by using the buccal and sublingual administration

routes. The buccal region of the oral mucosal cavity provides an appealing route of administration for systemic drug delivery. The mucosa has a rich blood supply and it is moderately penetrable. Patients are very happy with the oral cavity because the mucosa is relatively permeable and has a lot of blood, and the oral mucosa is tolerant of potential allergens because it doesn't have any langerhans cells.

Primary Highlights of Oral Mucosa: The mouth's mucosa is distinct from the rest of the gastrointestinal tract and has a more skin-like morphology. An outer layer of stratified squamous epithelium makes up the oral mucosa. Below this is a basement membrane called the lamina propria, and the sub mucosa is the innermost layer. There are three distinct types of oral mucosa. I. e. masticatory, lining and concentrated mucosa. The masticatory mucosa covers the gingival and hard sense of taste. It can withstand the abrasion and shearing forces of the masticatory process because it has a keratinized epithelium that is strongly attached to the underlying tissues by collagenous connective tissue. The coating mucosa covers any remaining regions with the exception of the dorsal surface of the toung.

The drug delivery's design and location are significantly influenced by the permeability characteristics resulting from regional differences in morphology. In general, the epithelia of the oral mucosa are somewhat leaky and lie somewhere in between the epidermis and the intestinal mucosa. The buccal mucosa is thought to be four to four thousand times more permeable than the skin. To ensure effective drug absorption, blood flow through a tissue is critical. The primary blood supply to the oral tissues comes from the external carotid artery. It branches into the lingual, maxillary, and facial arteries. Three principal veins collect blood from the capillary beds and feed the internal jugular vein. It is believed that blood flow through human oral mucosa is sufficiently rapid to not limit drug absorption even during disease. The oral mucosa's permeability to the drug and the drug's physicochemical characteristics (molecular weight, degree of ionization, lipid solubility) at the site of absorption are the two main factors that influence drug absorption from the mouth because the oral mucosa is a highly vascular tissue.

1.1 Advantage and Limitation:

The buccal route of drug administration has a number of advantages over oral administration, including:

- The drug is not exposed to the stomach's harmful acidic environment.
- The drug's therapeutic serum concentration can be achieved more quickly.
- The drug does not first pass through the liver before entering the general circulation.
- The mucosal permeability and local environment can be controlled and manipulated to accommodate drug permeation with the appropriate dosage form design and formulation.
- If necessary, delivery can also be stopped quickly.

Presystemic metabolism plays a significant barrier role for some medications. The enzymatic movement of the buccal mucosa is moderately low, and medication inactivation is neither fast nor broad. However, some drugs, particularly those that are peptide or protein-based, may be degraded by oral enzymes. The administration of bile salts and enzyme inhibitors like aprotinin, bestatin, puromycin, and bile salts together decreases the activity of proteolytic enzymes, resulting in a change in the peptide drug's conformation or the formation of micelles, and/or making the drug less susceptible to enzymatic degradation. The primary snags that medications meet when controlled through the buccal course get from the

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restricted ingestion region and the boundary properties of the mucosa. Although the drug's diffusion through mucus is not a rate-limiting step unless it specifically binds to the mucin or are large molecules, the mucin film may serve as a barrier. The rapid removal of the conventional delivery system, primarily through a lot of salivary flow, is another obvious obstacle that prevents this route from being used effectively. The issue of removal can be resolved with bioadhesive polymer.

2 FORMS FOR ORAL MUCOSAL DOSAGE

There are a variety of drug delivery systems that use the oral mucosa as a drug delivery site, such as chewing gum, fast-dissolving tablets, orodissolving films, and fast caps.

a) FDT, or Fast Dissolving Tablet: As a new drug delivery method, fast dissolving systems have recently begun to gain acceptance due to their ease of administration and improved patient compliance. They can also be used as a line extension for already-existing commercial products because they provide unique product differentiation. Direct compression, sublimation, melt granulation, molding, volatilization, and freeze drying are some of the methods that can be used to prepare FDTs. Zydis, orasolve, durasolv, flash dose, wowtab, flash tab, and others are examples of patented technologies. some drugs that are hard to dissolve in water and have variable bioavailability and bioinequivalence because they are hard to dissolve in water. The dissolvability of medication was expanded by different strategies to make a quick dissolving tablet like strong scattering strategy, by cogranulation with beta - cyclodextrin.

Because fast-dissolving systems dissolve or disintegrate in the mouth of the patient, the active ingredients compete with the patient's taste buds, making taste masking essential to patient compliance. Taste masking can be accomplished in a variety of ways, such as by adding sweeteners or by mass extruding eudragit E100. There have been a number of recent comparison studies between conventional and fast-dissolving formulations. If given the option, 93% of allergic patients would choose FDT formulations, according to an acceptance survey. b) Fast Dissolving Films: Despite their short dissolution/disintegration time, certain patient populations continue to be afraid of taking solid tablets and run the risk of choking. By developing a convenient dosage form for administration, recent advancements in novel drug delivery systems aim to enhance the safety and efficacy of drug molecules. Film that dissolves quickly is one option. It consists of a very thin oral strip that immediately releases the active ingredient once it is taken up by the mouth. Rapid film combines the advantages of liquid dosage forms (easy swallowing, rapid bioavailability) with those of tablets (precise dosage, simple application).

A patient simply places the delivery system on their tongue or any oral mucosal tissue. The film, which is immediately soaked in saliva, quickly hydrates and dissolves to release the medication for oral mucosal absorption. Hot melt extrusion, solid dispersion extrusion, rolling, semisolid casting, and solvent casting are all possible methods. Spence S.H. et al uncovered orally consumable movies that incorporate pullulan as a water solvent film framing specialist. Additionally, a film is being developed that may provide infants in improvised areas with the rotavirus vaccine. Using PVA as a polymer, Mashru R. C. et al. also created a salbutamol sulphate film that dissolves quickly. Renuka Sharma et al. created a taste-masked film utilizing HPMC and Eudragit EPO. Additionally, a number of patents have been assigned to oral water-soluble films.

c) Quick Caps Another kind of quick dissolving drug conveyance framework in

view of gelatine cases was created. Fast capsules, in contrast to conventional hard capsules, include various additives and gelation of low bloom strength to enhance the capsule shell's mechanical and dissolution properties. High drug loading, the possibility of solid and liquid filling, the absence of compression of coated taste-masked or extended release drug particles/pellets, good mechanical properties, simple manufacturing, mechanical stability, and the need for special packaging are all advantages of these rapidly disintegrating capsules.

d) Buccoadheshive Tablets and Film: There has been a growing interest in the creation of novel muco- adhesive buccal dosage forms in recent years. These are useful for both local drug targeting to a specific part of the body and systemic drug delivery. Due to their susceptibility to "dose dumping phenomena," water-soluble drugs are thought to be difficult to deliver in the form of sustained or controlled release preparations. Utilizing mucoadhesive polymers, efforts have been made to regulate their release process in order to achieve a once-daily dose treatment.

e) Prescription chewing gum: A number of advantages make medicated chewing gum a desirable alternative for drug delivery, including ease of administration, individually controlled active substance release, and efficient buccal drug administration for the treatment of local oral disease and systemic action. To provide a promising controlled release drug delivery system, chewing gum is primarily used.

Chewing gum with medicine can be used to relieve pain, stop smoking, treat travel-related illness, and freshen breath. Chewing gum was made with a gum that repels water. Additionally, a brand-new chewing gum device known as 3Tab gum has been developed. In vitro discharge investigation of biting gum requires extraordinary mechanical assembly and instrumental setting.

3 CONCLUSION

A drug delivery system that aims to increase patient compliance and convenience is more important than just getting the drug into the body. In order to meet the growing demand from patients for more convenient dosage forms, significant effort is being put into the development of novel dosage forms these days. These dosage forms are expected to gain popularity more quickly. Oral mucosal delivery is a convenient way to give medication to people who have trouble swallowing and to the general population. They also offer a chance to expand the product line in the market and extend the innovator's patent term.

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ADVANCEMENTS IN PHARMACOLOGICAL SCREENING TECHNIQUES FOR ANTIULCER AGENTS: A COMPREHENSIVE REVIEW

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Abstract - Globally, gastric hyperacidity and gastroduodenal ulcer are very common today. Stress, alcohol consumption, H. pylori infection, and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) have all been shown to generate reactive oxygen species (ROS), particularly hydroxyl radicals (*OH). Uncontrolled hydrochloric acid secretion from parietal cells of the gastric mucosa through the proton pumping H+ K+ ATPase causes hypersecretion of gastric acid, a pathological condition. In order to effectively heal a gastric ulcer, the modern treatment is to inhibit gastric acid secretion, promote gastro protection, block apoptosis, and stimulate epithelial cell proliferation. On the other hand, the majority of green pharmaceuticals have proven to be safe, clinically effective, more tolerable for patients, relatively less expensive, and competitive globally. They also reduce offensive factors.

Keywords: Pharmacological screening, gastric hyperacidity, and peptic ulcer.

1 INTRODUCTION

Disorders of the gastrointestinal tract (GI tract) are one of the most severe types of human diseases, resulting in maximum discomfort, morbidity, and limited mobility. One of these git disorders is peptic ulcer. A benign lesion of the gastric or duodenal mucosa known as peptic ulcer occurs when the mucosal epithelium is exposed to acid and pepsin. Stress, alcohol consumption, smoking cigarettes, H. pylori infection, and chemical and drug ingestion are just a few of the many causes. Peptic ulcers are brought on by a number of factors, including excessive alcohol consumption, smoking, and long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs). Due to mucosal damage, it has been established that free radicals play a role in the pathogenesis of peptic ulcer. The signs of peptic ulcer are as follows: severe upper abdominal pain and irritation. It may cause perforations in the intestinal wall if it is not treated appropriately.

Ulcer Peptique: It is a chronic inflammatory disorder characterized by ulceration in the upper gastrointestinal tract regions where parietal cells secrete hydrochloric acid 1 and pepsin.

Symptoms and signs: Here in peptic ulcer sicknesses patients can be asymptomatic or experience anorexia, queasiness, regurgitating, dying and smudging and heart consume or epigastric agony.

Epidemiology: Peptic ulcer diseases affect 5 to 10% of the general population over the course of a lifetime. There are approximately 3.9 million peptic ulcer patients in the United States, with between 200,000 and 400,000 new cases reported annually. The most common age group is between 50 and 70.

1.1 Etiology of Chronic Ulceration:

Heredity: Peptic ulcer patients frequently have a history of the disease in their family. This is especially true for duodenal

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ulcers that appear before the age of 20. Patients with gastric ulcers have three times the usual number, but relatives with duodenal ulcers have the same frequency as the general population.

Mucosal resistance versus acid pepsin: The mucosal digestion caused by acid and gastric juice pepsin is the immediate cause of peptic ulceration. However, the order in which this occurred is unknown. The normal stomach is clearly capable of resisting digestion by its own secretion, so acid and pepsin digestion cannot be the only factor. The phrase "acid plus pepsin Vs mucosal resistance" can be used to describe the idea of ulcer etiology.

Excessive gastric secretion: Only when acid and pepsin are present does an ulcer develop. They are never found in pernicious anemia patients or achlorhydric patients. Duodenal ulcers are more likely to be caused by acid secretion than by gastric ulcers. In clinical practice, peptic ulcer is the most prevalent gastrointestinal condition. Since synthetic drugs have side effects like arrhythmias, impotence, gynacomastia, and haematopoietic changes, their long-term use is restricted.

2 DIFFERENT FACTORS RELATED TO ACID SECRETION:

General factors: Vagal hormonal effect, histamine and epinephrine, insufficient circulation, shock and general ischemia increase the secretion.

- Constitutional and environmental factors i.e. sex, age, temperature, family history, social class, geographical differences; occupation may also influence the acid release.
- Local factors in stomach.

Aggressive factors: HCl, pepsin, refluxed bile, NSAIDs, alcohol, pancreatic proteolytic enzymes, ingested irritants, bacterial toxins, physiochemical trauma; all of these factors increase the acid secretion.

Digestive factors: Mucus, bicarbonates, blood flow, resolution of epithelium, the current status of therapy.

3 ANIMAL MODELS IN EXPERIMENTAL PEPTIC ULCER

Studies on animal models helps to understanding the aetiology and screening of anti-ulcer agents**.**

- Ulcers caused by ethanol
- Ulcers caused by cold restraint stress
- Stress-induced gastric ulceration
- Ulcers caused by pylorus ligation (PL)
- Ulcers caused by acetic acid
- Ulcers caused by histamine
- Ulcers caused by indomethacin
- Ulcers caused by serotonin
- Ulcers caused by aspirin
- Ulcers caused by reserpine

3.1 Alcohol Induced Gastric Ulcer:

Principle: The protein content of gastric juice is significantly increased by ethanol because alcohol increases gastric juice secretion and decreases mucosal resistance. This could be spillage on account of plasma protein in the gastric juice with debilitating of mucosal obstruction hindrance of gastric mucosa, this prompting peptic ulcer.

Procedure: Pale skinned person rodents of either sex gauging between (150-200 gms) are isolated into six gatherings of creatures in each gathering. The animals have free access to water during their 24-hour fast. Either a standard or a test drug is given to the animals. Each animal is given 1 ml/200 gm of 99.80% alcohol p.o. one hour later. The stomach is isolated, cut along the greater curvature, and pinned onto a soft board one hour after alcohol administration. Each gastric lesion is measured in millimeters. The length of the control-mean lesion index of text divided by the mean lesion index of the control is used to calculate the percent inhibition.

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The gastric ulcer caused by H. pylori: Principle6: It is a gram-negative bacteria that most people, especially the elderly, have in their gastric and duodenal mucosa. They split into ammonia while they are in the mucosa, elevating the mucosa's local region with high alkalinity. As a result, they significantly aid in the development of peptic ulcers.

Procedure: Pale skinned person Wistar rodents of either sex gauging between (150-200 gms) are separated into five gatherings of six creatures in bunch. Albino rats are fasted for 24 hours in separate cages using this method. Coprology was being avoided with care. 30 minutes before the pyloric ligation, either the control vehicle, the standard drug, or the test drug is given. Under light ether sedation, the midsection is opened and the pylorus was ligated. After that, the abdomen is sutured. After ligation, the animals are sacrificed four hours later with an excess of anesthetic ether. The stomach is then dissected, the gastric juice is collected, and the tubes are centrifuged for ten minutes at 1000 rpm to record the volume. A pH meter measures the gastric juice's pH. After that, the contents are examined for free and total acidity. After that, the stomachs are rinsed under running water to check for ulcers in the glandular area.

The numbers of ulcers per stomach are noted and severity of the ulcers scored microscopically with the help of hand lens (10x) and scoring was done as per Kulkarni (1987).

0 = Normal stomach

0.5 = Red coloration

1 = Spot ulcers

1.5 = Haemorrhagic streaks

2 = Ulcer > 3 mm but > 5 mm

3 = ulcers > 5 mm

Percentage protection = 100- ut / uc × 100

Mean ulcer score for each is expressed as ulcer index. The percentage protection is calculated using the above formula.

where, ut = ulcer index of treated group. uc = ulcer index of control group.

3.2 Stress- Induced Gastric Ulcer:

Principle: Burns and trauma, as well as prolonged anxiety, tension, and emotion, severe physical discomfort, hemorrhage and surgical shock, and severe gastric ulceration, can all contribute to stress. It is difficult to understand how gastric ulcers work. Recent studies have demonstrated that mucosal antioxidant enzymes like super oxide, dismutase, and peroxides are disrupted in response to resistant cold stress, which results in severe hemorrhage ulcers. The mechanism of ulceration in this instance ought to be distinct from that of ulcers caused by other factors because this stress condition is primarily caused by physiological discomfort. The stress results in the formation of highly reactive OH* radicals, which are catalyzed by metal and cause oxidative damage to the gastric mucosa. Following the oxidative damage caused by gastric peroxides and the activation of superoxide dismutase, the Herber weiss reaction occurs between O2 – and H2O2.

Procedure: Pale skinned person Wistar rodents of either sex gauging between (150-200 gms) are separated into five gatherings of six creatures in bunch. Cold resistance stress (CRS) is applied to rats that have been fasted for 18 hours. The rats are strapped to a wooden plank and kept at 4 to 6 degrees Celsius for two hours. After that, the animals are killed by dislocating their cervical spines, and the ulcers on their dissected stomachs are scored.

Gastric ulcer caused by aspirin: Principle5: NSAIDs hinders the PG combination of gastric mucosa, PG gives cytoprotection. Damage is caused when leukotriene synthesis is increased. In

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addition, aspirin inhibits gastric peroxidase and may raise mucosal H2O2 and hydroxyl ion concentrations, resulting in oxidative mucosal damage.

Procedure: Each sexe of albino rats weighs between 150 and 200 grams. They are divided into five groups of six animals each. The animals observe a 24-hour fast. The test drug in differing focuses in view of the plan of the examination is directed orally in 2% gum acacia arrangement brief preceding ibuprofen at portion of 200 mg/kg. After four hours, the rats are killed with ether, an anesthetic, and their stomachs are cut open. for the purpose of identifying gastric lesions.

Indomethacin (IND)- incited gastric ulcers: Principle9: Gastric lesions were produced linearly on mucosal folds and had the appearance of mucosal erosions when indomethacin (20 mg/kg) was administered orally. These lesions were primarily found in the glandular portion of the stomach and few or none in the antrum.

Procedure: IND (20 mg/kg BW) given intravenously as a single dose suspended in 0.5 percent carboxymethyl cellulose. dose to cause gastric ulcers 30 minutes after the test or regular medication treatment. Lesions in the gastric mucosa were scored after the animals were killed after 5 hours. The length of the ulcer was measured along the greater diameter after the areas of the ulcer had been identified. One millimeter of an ulcer was considered to be the number of hemorrhagic spots. By dividing the total length (in mm) of the ulcers in all of the animals by the total number of animals, the mean ulcer size was determined.

3.3 Gastric Ulcer Induced by Histamine:

Principle: It is known that both the vasospastic action of histamine and increased gastric acid secretion are involved in histamine-induced gastric ulceration.

Procedure: For 36 hours, 300-400 g guinea pigs were fasted. prior to the experiment, the animals were given free access to water and divided into two groups of six each. I.p. caused gastric ulceration. administration of 50 mg of Sigma USA histamine acid phosphate. base.). 5 mg is used to protect the animals from histamine toxicity. of hydrochloride promethazine was injected intravenously. to each animal 15 minutes after administering histamine. The vehicles used to test drugs or control (Dist. water) were taken orally 45 minutes prior to administering histamine.

Gastric ulcer caused by sertraline: Principle: Reserpine-prompted gastric ulceration has been credited to the degranulation of gastric pole cells and ensuing freedom of receptor which is accepted to be a cholinergacally intervened.

Procedure: For 24 hours, adult albino rats were fasted. following free access to water. Reserpine was given to four groups of six rats each via intramuscular injection (5 mg/kg). 30 min after the organization of the test medication or control vehicle (Refined water) intraperitoneally. After 18 hours, all of the animals were killed, their stomachs were opened along the greater curvature, and the "ulcer index" was the sum of the lengths (mm) of all lesions for each rat.

4 CONCLUSION

Aspirin-induced ulcer model, stress-induced ulcer model, Pylorus lighted-induced ulcer model, ethanol-induced ulcer model, acetic acid-induced ulcer model, cold-resistant stress-induced ulcer model, histamine-induced ulcer model, and others are some of the methods used to evaluate green pharmaceuticals as anti-ulcer agents. Using the aforementioned methods, both natural and synthetic products can be scientifically evaluated to determine their therapeutic efficacy.

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REVITALIZING STEVIA PLANT REGENERATION VIA CALLUS CULTURE TECHNIQUES

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Abstract - Stevia rebaudiana Bertoni is typically propagated by seed, cuttings, or clump division, which results in a limited supply of seed material of both quality and quantity. In this study, the callus culture method was tried to multiply plants quickly for high-quality seed material. Callus acceptance and duplication medium was normalized from nodal as well as leaf sagments. On Murashige and Skoog medium supplemented with 6-benzyl amino purine and naphthalene acetic acid, calluses can be maintained. Murashige and Skoog medium supplemented with naphthalene acetic acid (2.0 mg/l) and 6-benzyl amino purine (2.0-3.0 mg/l) treatments resulted in the greatest callus induction. However, for callus induction, Murashige and Skoog medium with 2.0 mg/l 6-benzyl amino purine and 2.0 mg/l naphthalene acetic acid was found to be the best. Murashige and Skoog medium with 2.0 mg/l 6-benzyl amino purine and 0.2 mg/l naphthalene acetic acid was found to have a higher regeneration frequency. On 14 Murashige and Skoog strength with 0.1 mg/l indole-3-butyric acid added, regenerated plants had stronger roots. With a 63% survival rate, the rooted plantlets successfully hardened in tera care medium. Regardless of the season, i.e., the external environmental conditions, the developed protocol can be used for large-scale mass production of planting material that is true to type.

Keywords: Regeneration, stevia, glucose, glycoside, explant, hardening, callus.

1 INTRODUCTION

Stevia rebaudiana Bertoni is a perennial herb that grows in Paraguay and Southern Brazil. It is a member of the Asteraceae family. The plant's glycosides, which have chemical and pharmacological properties that make them suitable for human consumption as a natural caloric-free agent, are found in the plant's leaves. Diterene glucosides are one hundred to four hundred times

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sweeter than glucose. The eight kinds of glycosides are rebaudioside A, rebaudioside B, rebaudioside C (dulcoside A), rebaudioside D, rebaudioside E, rebaudioside F, steviolbioside An and dulcoside An are recognized. Since the early 1970s, these sweets have been used on a commercial scale in Japan. Stevia cultivation has recently gained commercial importance in Brazil after its liberation for human consumption. In the years to come, stevia will advance to become the best substitute for table sugar. Stevia is grown in several nations, including China, Canada, Brazil, South East Asia, and Japan. Seeds or cuttings are used to reproduce the plant. Although althogh seed propagation is a very common method, seed is ineffective due to the flowers' self-incompatibility and low fertility Because a donor plant only produces a small number of new plants simultaneously, cutting propagation is limited. In subtropical climate regions of India, stevia can be grown. Hence, taking into account its extension and future need of establishing material, this analysis was directed to normalize convention for quick augmentation of Stevia through callus culture strategy.

Explants from the Stevia plant were obtained by collecting nodal segments and leaves. From collected explants, nodal segments and leaves measuring approximately 1.5 cm in length were isolated. After being washed for approximately 30 minutes in running tap water, the explants were treated for 5 minutes with a 10% detergent solution. By thoroughly washing with double-glass distilled water, the traces of detergent were removed. After that, a 0.1% mercuric chloride solution was used to surface sterilize the explants for three minutes under aseptic conditions in a laminar air–flow cabinet. After that, the explants were rinsed four times with sterilized double glass distilled water. By trimming both ends, sterilized nodes were further reduced to 0.8 cm in size. In the case of leaf explants, sterilized leaves were divided into pieces measuring 0.5 cm2 for use in the medium's inoculation.

On nutrient Murashige and Skoog (MS) medium supplemented with 6-benzyl amino purine (BAP- 1, 2, and 3 mg/l) and naphthalene acetic acid (NAA- 0.2 and 2.0 mg/l), the prepared explants were inoculated. In an air-conditioned culture room, the cultures were inoculated at a temperature of 26°C and exposed to 1000 lux of fluorescence cool tube light. For the purpose of regenerating shoots, the calluses obtained from various treatments were recultured in S3 (MS supplemented with 2.0 mg/l BAP and 0.2 mg/l NAA). For in vitro rooting, the shoots harvested from regeneration medium were excised and transferred to rooting

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medium. We tried MS liquid medium at half and quarter strength. Different concentrations of indole-3-butyric acid (IBA) were added to each medium. 0.1, 0.5, 1.0, and 0.05 mg/l). Perceptions on foundation and multiplication were recorded following three and a month of brooding of societies, separately, while if there should be an occurrence of establishing, it was recorded following three weeks.

The rooted plantlets were moved into polyethylene bags that were filled with four different kinds of potting mixtures, such as tera care; soil: care for Tera soil: Soil and mold on leaves: leaf mold: Tera provides equal care to each. After three weeks, survival rates of plantlets were recorded.

The endurance pace of plantlets was affected by preparing combinations. Tera care potting medium had the highest survival rate of plantlets (63%). The survival rate of plantlets was reduced when soil or leaf mold were included in tera care.

Auxin is the essential supplement that must be added to the basal medium to provide inorganic ions and sugars for the culture of a number of callus tissues. Auxin was also mentioned by Navarro et al. as a necessary supplement for the induction of calluses. Other researchers have demonstrated that the addition of cytokinin to the auxin medium has an additive effect on tissue growth in a variety of plant species[6]. In the current investigation, it was also found that incorporating BAP helped the callus grow.

Root formation was enhanced when sufficient amounts of Auxin were added to the MS medium. On 14 strength MS medium supplemented with 0.1 mg/l IBA, we observed a more favorable rooting response in our studies. The results of this study are consistent with those of Ferreira and Handro, who also found that root formation was optimal at 0.1 mg/l IBA. On the other hand, Tadhani et al. reported that Stevia's rooting response was better on MS medium with 1 mg/l IBA added. According to the findings of this study, the variation may be caused by the explant's origin, a shift in the microclimate, or a variation in the strength of the rooting MS medium.

2 CONCLUSION

Before being transplanted into the field, in vitro plants must be hardened. The survival of the plantlets was better with potting mixture tera care in this study. The potting mix may assist in providing sufficient aeration and improved rooting grip. Plant species and the potting mix used to raise in vitro plants in a greenhouse also play a role in in vitro plant survival. The remaining reports on peat-based potting mixtures: sand, perlite, soil:

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vermiculite, for example were reported for greenhouse-based in vitro plant establishment. True-type and disease-free planting materials can be produced on a large scale at any time of year with the developed method.

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EUCALYPTUS GENUS: A COMPREHENSIVE REVIEW OF PHYTOCHEMICAL CONSTITUENTS AND PHARMACOLOGICAL ACTIVITIES

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Abstract - In the Myrtaceae family, Eucalyptus is a diverse genus of flowering trees and shrubs. From plants belonging to the eucalyptus genus, various chemical components like Sideroxylonal C, (+)-oleuropeic acid, cypellocarpins A, B, and C, cypellogins A, B, and C, Leptospermone, Isoleptospermone, grandinol, and various essential oils have been isolated. It has been reported that a number of eucalyptus species have potent pharmacological effects against diabetes, hepatotoxicity, inflammation, cancer, and other conditions. The purpose of this review article is to bring together all of the most recent information on the phytochemical and pharmacological activities of Eucalyptus species that have been carried out in a variety of ways.
Keywords: Eucalyptus's phytochemical and medicinal properties.

1 INTRODUCTION

Eucalyptus is a large genus of evergreen aromatic tresses, rarely shrubs (mallees), native to Australia, Tasmania, New Guinea, and the islands nearby. There, they make up a significant portion of the forest vegetation and give it its distinctive appearance. Due to their economic value, various species of Eucalyptus are cultivated, particularly in warm temperate and subtropical regions.

The rapid growth of Eucalyptus species (Family: Myrtaceae) is remarkable. A few types of them, right at home, accomplish monstrous sizes and are among the tallest trees of the world. Despite the fact that the majority of the species do not produce gum but rather an astringent, they are commonly referred to as "gum trees." a substance known as "kino" that is toxic.

Primary species: Eucalyptus comes in over 500 different species. The majority of Eucalyptus species are Amygdalina, australiana, botryoides, calophylla, camaldulensis, citriodora, cladocalyx, consideniana, cypellocarpa, dives, gigantea, globulus, gomphocephala, grandis, gunnii, incrassate, kino, largeflorens, lesoue

1.1 Taxonomical Classification:

Kingdom	: Plantae
Subkingdom	: Tracheobionta
Super division	: Spermatophyta
Division	: Magnoliophyta
Class	: Magnoliopsida
Subclass	: Rosidae
Order	: Myrtales
Family	: Myrtaceae
Genus	: *Eucalyptus*

2 PHYTOCHEMICAL AND PHARMACOLOGICAL ASPECTS

1. Alba eucalyptus:

Components of a chemical: The main chemical component of Eucalyptus albens is sideroxylonal C, which was isolated from the flowers. Physicochemical Activity: Sideroxylonal C represses human plasminogen activator inhibitor type-1 with next to no massive impact on human tissue plasminogen activator 2.

2. Chemical Components of Eucalyptus amplifolia: The primary chemical component is the acylphloroglucinol-

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monoterpenes Euglobal-Am-II, Euglobal-Am-IVb, and Euglobal-Am-VII. Physicochemical Activity: Epstein-Barr virus (EBV) 3 is significantly inhibited by Euglobal-Am-II, which was isolated from the leaves of Eucalyptus amplifolia.

3. Caudulensis eucalyptus:

Components of a chemical: Aromandrene Myrtenal, Borneol, Camphene, Carvacrol, Citronellal, and Cryptone-- Terpenyl acetate are essential oils. 4, Flavonoids (Apigenin, Chrysin, Flavone, Luteolin, Eriodictyol, Hesperetin, Naringenin, and Pinocem-brin) and 5 triterpenoids (Oleanolic Acid, Maslinic Acid, Camaldulic Acid, and Camaldulensic Acid) make up the majority of E. camaldulensis 6-10's composition. Physicochemical Activity: Antimicrobial: A chewing stick made of the bark of Eucalyptus camaldulensis is commonly used. The inhibition zones in the bark extract of Eucalyptus camaldulensis are comparable to those of standard antimicrobials.

4. Eucalyptus citriodora:

Components of a chemical: This species mostly contains essential oils (Cineole, Citronellal, and Citronellic Acid) 15, Sterols (9-Sitosterol).

Physicochemical Activity: Analgesic: It has been demonstrated that the essential oil of Eucalyptus citriodora induced analgesic effects in both models, suggesting both peripheral and central actions, by using acetic acid-induced writhes in mice and hot plate thermal stimulation in rats.

Antifungal properties: The antifungal properties of the volatile oil derived from Eucalyptus citriodora leaves were diverse. The most effective components against fungal pathogens like Tricophyton rubru, Trichophyton mentagrophytes, Microsporum canis, Epidermophyton floccosum, and Epidermophyton stockdale are eucalyptus oil, camphor, menthol, and thymol oil.

Anti-inflammatory: The anti-inflammatory activity of Eucalyptus citriodora was demonstrated by the inhibition of rat paw edema induced by carrageenan and dextran, neutrophil migration into rat peritoneal cavities induced by carrageenan, and vascular permeability induced by carrageenan and histamine. Essential oil extracted from Eucalyptus citriodora. Inhibition of Bone Resorption: Monoterpenes and essential oil of eucalyptus inhibit rat bone resorption effectively.

Repellant from nature: Citriodiol, a natural ingredient in lemon Eucalyptus extract, has been shown to repel mosquitoes, stable flies, and midges [19]. It eliminates the Ixodes ricinus, which is capable of transmitting a number of microorganisms.

5. Cladocalyx of Eucalyptus:

Components of a chemical: The primary chemical components of this species 20 are cladocalol, a triterpene that was isolated from the leaves, ursulolactone acetate, ursolic acid, 3-beta-acetate-12, 20-lupadien-28-oic acid, beta-sitosterol, and eucalyptine. Physicochemical Activity: The myeloid leukemia cell line HL-60 is cytotoxically affected by cladocalol and its derivatives.

6. Eucalyptus cypellocarpa:

Components of a chemical: The major chemical components of Eucalyptus cypellocarpa 21's leaves are acylated flavonol glycosides, cypellogins A, B, and C.

Physicochemical Activity: In vitro, Cypellogins A, B, and C demonstrated potent antitumor activity. In vivo two-stage carcinogenesis induced by nitric oxide and TPA (12-O-tetradecanoyl phorbol 13-acetate) on mouse skin was also suppressed by these substances.

7. Globules of eucalyptus:

Components of a chemical: -Pinene, -Pinocarvone, -Pinene) 23-25 Hydrocarbons (4-Hydroxytritriacontane-

16, 18-dione, 16-Hydroxy Btritriacontanone, n-Tritriacontane 16, 18-dione), Macrocarpals H, I, and J 26, and Geranyl acetate are the primary chemical constituents.

Physicochemical Activity: Antibacterial: A 50% EtOH-soluble material extracted from the dried leaves of Eucalyptus globulus shows appreciable antibacterial activity against S. mutans Ingbritt and P. gingivalis ATCC 33277 (causes dental caries and periodontal disorders) with MIC values of 12.5 and 6.25 g/ml 27. This material has antibacterial activity against oral pathogenic microorganisms with MIC values ranging from 0.20 micrograms/mL.

The minimum inhibitory concentrations of Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, and Candida albicans in dried residue of methalonic extract of Eucalyptus globulus leaves were 5.0, 10.0, 10.0, and 1.25 mg/ml, respectively 28. The macrocarpals H, I, and J phenoglucinol-sesquiterpene-coupled compounds demonstrated potent antibacterial activity and an inhibitory effect of glucosyltransferase 29. Additionally effective against the reference strains of Staphylococcus aureus, Saturia hortensis L., and Teucrium polium L 30 are the ethanolic extracts of Eucalyptus globulus. Pseudomonas aerugenosa was the target of the majority of the extracts of Eucalyptus globulus's high antibacterial activity.

Six Gram-positive bacteria (Staphylococcus aureus, MRSA, Bacillus cereus, Enterococcus faecalis, Alicyclobacillus acidoterrestris, and Propionibacterium acnes) and a fungus (Trichophyton mentagrophytes) were significantly inhibited in growth by the methanol-dichloromethane extract of Eucalyptus globulus. By exposing the tested periodontopathic bacterial strains to 0.2% oil of Eucalyptus globules for thirty seconds, they were completely eradicated. From 200 clinical specimens of patients with respiratory tract disorders, the antibacterial activity of Eucalyptus globulus leaf extract was evaluated against Staphylococcus aureus, Streptococcus pyogenes, Streptococcus pneumoniae, and Haemophilus influenzae.

Antidiabetic: Traditionally, eucalyptus globulus is used to treat diabetes. Streptozotocin-treated mice lost less weight and had less hyperglycemia when Eucalyptus globulus (62.5 g/kg) and water (2.5 g/L) were added to their diets. In mice's abdominal muscle, an aqueous extract of Eucalyptus globolus (AEE) (0.5 g/L) increased 2-deoxy-glucose transport by 50%, glucose oxidation by 60%, and glucose incorporation into glycogen by 90%. In intense, 20 min brooding, 0.25-0.5 g AEE/L evoked a stepwise 70-160% improvement of insulin discharge from the clonal pancreatic beta-cell line (BRIN-BD11). According to these findings, Eucalyptus globulus is a potential source for the discovery of new oral agents for upcoming treatment and an efficient antihyperglycemic dietary supplement for diabetes treatment.

Antiplaque: Eucalyptus globulus might be valuable in repressing dental plaque development 35.

Antitumor: On the 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced Epstein-Barr virus early antigen (EBV-EA) activation test system, the antitumor-promoting activity of Euglobals Ia1, Ia2, Ib, Ic, IIa, IIb, IIc, III, IVa, IVb, V, and VIII was tested in vitro. Following euglobals Ib, IIa, Ic, Ia1, and Ia2 36, euglobal-III displayed significant inhibitory activity. In THP-1 cells, the LPS-induced nuclear translocation of NF-kappa B is inhibited by eucalyptus globulus oil.

Antiviral: Using a short-term in vitro assay, the inhibitory effects of twelve euglobals from Eucalyptus globulus and twenty-six related compounds on the activation of the Epstein-Barr virus were investigated. The majority of euglobals with monoterpene structures and euglobal-III with strong inhibitory activity

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38 were found. The oil of eucalyptus globulus has antiviral properties against the herpes simplex virus (herpes simplex viruses 1 and -2).

Antifungal: With concentrations of 100%, 75%, and 50%, freshly prepared camphor oil from Eucalyptus globulus completely eradicated human facial demodicidosis 40. On Sabouraud's destrose agar medium, Eucalyptus globulus leaf extract and oil demonstrated antifungal activity by gradually inhibiting the growth of Malassezia furfur.

Antihistaminic: IgE-dependent histamine release from RBL-2H3 cells was inhibited by ethanol extract of Eucalyptus globulus fruits and leaves and hexane extract of Eucalyptus globulus leaves.

Anti-inflammatory: 1,8-cineole, a major component of Eucalyptus globulus volatile oil, is a potent cytokine inhibitor that may be suitable for the long-term treatment of bronchial asthma and other steroid-sensitive conditions 43. It has been demonstrated that the essential oil of Eucalyptus globulus induced analgesic effects in both models using acetic acid-induced writhes in mice and hot plate thermal stimulation in rats, indicating both peripheral and central actions. The inhibition of rat paw edema induced by carrageenan and dextran, neutrophil migration into rat peritoneal cavities induced by carrageenan, and vascular permeability induced by carrageenan and histamine all demonstrated the anti-inflammatory effects of essential oil extracts from the Eucalyptus globulus.

3 CONCLUSION

According to the extensive literature review, Eucalyptus species are a significant source of numerous pharmacologically and medicinally significant chemicals, including essential oils and terpenoids used in aromatherapy. Analgesic, antifungal, anti-inflammatory, antibacterial, antiidiabetic, antioxidative, antiviral, antitumor, antihistaminic, cytochrome p450 inhibitor, and hepatoprotective properties of various Eucalyptus species have also been extensively studied. There is little evidence that aromatherapy is effective in patients undergoing medical interventions, despite the fact that it is pleasant, inexpensive, and has few side effects (with the exception of rare allergies).

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EXPLORING THE MEDICINAL PROPERTIES AND SYNTHETIC STRATEGIES OF PYRIMIDINE DERIVATIVES: A COMPREHENSIVE REVIEW

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Abstract- Pyrimidine chemistry is a blossoming field. Various strategy for the combination of pyrimidine and furthermore their assorted responses offer tremendous extension in the documented of restorative science. These researches have been sparked by the fact that pyrimidines can be used as synthons for a variety of compounds with biological activity. The purpose of this review article is to examine the published research as well as the chemistry and biological functions of pyrimidines over the past year.
Keywords: Pyrimidines, UV and IR spectroscopy, chemistry, and therapeutic potential.

1 INTRODUCTION

Pyrimidines are the most important six-member heterocyclic with two nitrogen atoms. Of the three isomeric diazines, pyrimidines are present. The nucleic acid hydrolyses have yielded a number of pyrimidines, mostly uracil, thymine, and cytosine. Pyrimidines ring is also found in vitamin B1, barbituric acid (2, 4, 6-trihydroxy pyrimidine) and its several derivatives, such as Veranal), which are used as hypnotics.2 Numerous reports have appeared in the literature that highlight the chemistry and uses of Pyrimidines. The nucleic acids are essential constituents of every cell and, as a result, of all living matter. Cytosine is found to be present in both types of nucleic

Pyrimidine preparation: Manufactured procedures' of Pyrimidines have involved four primary courses in light of the buildup of two parts as outlined by VI-IX; The condensation of three carbon units with an N-C-N fragment, which is illustrated by VI, appears to be the most widely used strategy. This method has been dubbed the common synthesis due to its general applicability to the synthesis of a wide range of pyrimidine derivatives. The fact that one or both of the group of three carbon atom fragments can be present as an aldehyde, ketoaldehyde, -keto esters, malonic ester, -aldehydo, or -keto nitrile, as well as many other combinations of these groups or their masked derivatives, allows for a great deal of flexibility in this synthesis.

Acetyl acetone is a great example because it readily reacts with formamidine, guaidine, urea, or thiourea6 to produce, dimethyl pyrimidines. The nitrogen-containing fragment can be an amidine, urea, guanidine, or thiourea.

Acetone and this reagent with toluene sulphonic acid as catalyses yield 4-methyl pyrimidines. Ethyl -aminocrotonate undergoes an extremely simple reaction with phenylisocyanate or methyl isocyanate to form an intermediate ureido derivative that undergoes cyclization as treatment with base.8 The condensation of maloenonitrile with amidines such as formamide or benzamidine results

The 4, 6 di-substituted pyrimidines and 2 amino 4, 6 di-substituted pyrimidines that were produced when sodium hydroxide and chalcone were combined in a reaction.

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2 MOLECULAR SPECTRA OF PYRIMIDINES

U.V. spectra of pyrimidines: The position, number, and nature of any chromophoric substituent that is attached to a pyrimidine, as well as the ionic species that are present in the solution being measured, will all have an impact on the UV spectrum of pyrimidines. The state of the nucleus (full aromatic, partially reduced, or completely reduced) is also a factor. Cyclohexane exhibits pyrimidine ultraviolet absorption in two bands centered at 243 and 298 nm. On account of the hypsochromic shift observed when switching solvents from cyclohexane to water, the second band is attributed to the electronic transition from a nitrogen lone pair non-bonding orbital to an empty -orbital, or an n to * transition. Since the lone pair engages in hydrogen bonding in water, the absorbed radiation must be of higher energy (i.e., shorter wavelength) in order to break the hydrogen bonds and bring about the A transition from the occupied orbital of the ring with the highest energy to the empty orbital of the ring with the lowest energy is attributed to the more intense band at 243 nm. Similar to the transition that is responsible for the band at 250 nm in benzene, these bands are unaffected by solvent changes. In most cases, substituents that release electrons cause a bathochromic shift in the n* band, whereas substituents that withdraw electrons do the opposite.

I.R. pyrimidine spectra: The primary cause of the I. R. spectra is a vibrational transition; numerous substitutes with isolated double bands or single bands produce characteristic absorption bands with a limited frequency.

Their spectra helped quantitatively study the tautomerism of pyrimidines, pyrimdinethiones, and pyrimidines in the solid state or in non-protic solvents and provided reference data for the identification of certain attached groups. It is well established that six membered hetro- aromatic "hydroxy" compounds with oxygen in to a ring nitrogen provide N-H stretching bands in the range 3360-3420 cm-1, whereas those with oxygen in to a ring nitrogen have seen bands in the range 3415-3445 cm-1. Naturally, pyrimidin-2-one provides strong absorption bands for C=O and N-H band stretching vibration. The symmetric and anti-symmetric vibrations that pyrimidin-2(and 4)-amine absorb at distinct lover frequencies (3300 cm-1) are shown by two 3500cm-1 patterns.

The IR spectra of 2-(3-phenyl- 4-formyl pyrazol- 1-yl)- 3- (4-methyoxypheyl)- 1, 8 napthopyrimidine were examined by Mogilaian et al.20. The IR spectra of these compounds had absorption bands at 1687 and 1608 due to C=O and C=N stretching frequencies. The structure of these compounds was confirmed as the basis of spectral studies.

Due to the respect for N-H, C=O, and C=S, Alagarsamy et al21 reported that the I.R. spectra of 2-Allylamino- 1, 3, 4-thiazolo (2, 3-b), 6, 7- dimetyl thizeno-(3, 2-e) pyrimidine -5 (4H)-one contained absorption bands at 3280, 1690, and 1180.

According to Rinde et al.22's analysis of the I.R. spectrum of 6-*2' hydroxyl-3'-(2'- aryl thiazol- 4'-substituted phenyl]-4-aryl-2-amino pyrimidines, these compounds exhibit an absorption bond at 2965, 2950 (-NH2), and 3040 (O-H phenolic).

Nuclear Magnetic resonance spectroscopy: In 1960, the first proton NMR spectrum of pyrimidine was published, and the results were later confirmed. As would be expected, the forer proton's relative shielding is H-2>h-4=H-5 [S (CDCl3)] The spectrum shows little variation between a pure liquid and a diluted carbon tetrachloride solution. The methyl protons and ortho or para ring protons of the three mono-c-

methylpyrimidines do exhibit long-range coupling. In CDCl3, for instance, 2-methyl pyrimidine has 0.6 Hz and 4-methyl pyrimidine has 0.4 Hz.

The majority of the other pyrimidines have normal NMR spectra because they are mono substituted by a non-tautomeric group. As a result, the doublet and triplet of 2-substituted pyrimidines are widened by coupling to the nitrogen adjacent to it; The 2-substituent's nature naturally affects the chemical shift and J4.5: Compare 2-carbonitrile with pyrimidine (1; R = (Me2CO) / (CN) 9.04, H-4/6; 7.86, J4.5, 5.1 Hz,H- 5] as well as 2-bromopyrimidine (one; R equals Br) * (Me2CO): 8.72, H-4/6; 7.57, J4.5 4.8 Hz, H- 5].

Spectra of mass for pyrimidines: Pyrimidines and quninazolines typically have straightforward mass spectra. Ionized acetylene is produced by the predominant fragmentation mode of pyrimidines, which is the double loss of HCN. 26, as base peak, it is unclear whether C- 2 or C- 4 is involved in the initial loss of HCN. The pyrazole radical cation (I) or possibly an imidazole appears to be the product of the first loss in pyrimidine-2-amine, both of which are known to fragment according to the subsequent pattern. In contrast, pyrimidine-4-amino and its derivative follow a significantly altered and quite complicated pattern, with uracil(II, R=H) and thymine(II,R=CH3) undergoing the retro-Diels-Alder The subsequent division follows a logical pattern. At least three pathways produce cytosine fragments, all of which involve the initial loss of CO. However, barbituric acid moves forward by logically losing 2XHNCO in the main.

2.1 Pyrimidines' Biological Effects Include

Efficacy against bacteria: In order to test for antimicrobial activity, Saundane et al.26 synthesized 2- (2', 5' substituted indolideneamino- 3'-yl)- 4, 6- diaryl pyrimidines (I) and 2- [2', 5'- substitutedindole- 3'- yl) (phenyl azo) methylene imino]- 4, 6- Diaryl pyrimidine(II). The compound was tested for antifungal activity against A. niger and A. flavus using the cup plate method at a concentration of 1000 g/ml in DMF against the gram-negative bacteria E. coli and the gram-positive bacteria S. aureus.

Activity against Inflammation: The anti-inflammatory properties of three substituted derivatives of 4-phenyl- 2-thioxobenzo [4' 5] thieno [2, 3-d] pyrimidine, synthesized by Vega et al.39, were tested against rates of carrageen-induced edema. They were compared to those for piroxicam, ibuprofen, and acetyl salicylic acid, which were chosen as the reference standard.

Efficacy against Cancer: Alagarsamy et al. 41 reported that some substituted (1, 3, 4) thiadiazolo thieno[3, 2-e]pyrimidin 5(4H)-enes had anticancer activity. The substance was effective against lung, breast, and other types of cancer.

Analgesic Effect: Rathod et al.45 created 2-aryl amino- 3-aryl- 5-methyl- 6-(substituted) pyrimidin-4 (3H)- ones. The tail flick method on albino rats and the writing method on albino mice were used to test each of the synthesized compounds for their analgesic properties.

Activity as a diabetic: The hypoglycemic activity of fifty synthesized azolopyrimidine derivatives and compounds was evaluated by Desenko et al.

Diverse activities: A little library of 20 tri-subbed pyrimidines was combined by Anu et al 52 assessed for their in vitro enemy of malarial and hostile to tubercular exercises. In vitro anti-malarial activity against Plasmodium falciparum in the range of 0.25-2 g/ml has been demonstrated by 16 of the screened compounds, and anti-tubercular activity against Mycobacterium tuberculosis in the range of 12.5 g/ml has been

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demonstrated by 8 of the screened compounds.

3 CONCLUSION

Because of extensive research; The chemistry of pyrimidines continues to be a flourishing field, and it would also be fascinating to see the development of pyrimidines as a potentially active therapeutic compound.

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DATABASE OF THE NUCLEAR RECEPTOR SUPERFAMILY: A COMPREHENSIVE RESOURCE FOR RESEARCHERS

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Abstract - A comprehensive database of the Nuclear Receptor (NR) Superfamily-Ligand is the project's goal. One of the most significant families of drug targets in pharmaceutical development is the Nuclear Receptor Superfamily. Nuclear Receptor (NR) Superfamily-Ligand is a brand-new public chemical genomic database that primarily focuses on the correlation of NR and ligand information. In addition to chemical information on ligands and access information to various NR-related web databases, it provides correlation data between NRs and their ligands. In a relational database, these data are linked to one another, making it simple for researchers working on NR-related drug discovery to find this information from biological or chemical starting points. Structure similarity search functions for the NRs and their ligands are included in the NR Superfamily-ligand database. As a result, correlation maps between the searched homologous NRs (or ligands) and their ligands can be provided by the database; By concentrating on inferred candidates for NR-specific drugs, we can increase our understanding of their interactions and enhance our efforts to design drugs.
Keywords: Docking, NR, Ligands, and Database.

1 INTRODUCTION

Nuclear receptors are a class of proteins that are found inside cells and are responsible for sensing the presence of certain molecules and steroid and thyroid hormones in the field of molecular biology. In response, these receptors collaborate with other proteins to control the expression of particular genes, thereby controlling the organism's metabolism, homeostasis, and development. One of the most common classes of transcriptional regulators in animals (metazoans) are nuclear receptors. Nuclear receptors are referred to as transcription factors because they can directly bind to DNA and control the expression of adjacent genes, allowing them to regulate a wide range of functions, including homeostasis, reproduction, development, and metabolism. Nuclear receptors can only regulate gene expression when a ligand—a molecule that alters the behavior of the receptor—is present. More specifically, when a ligand binds to a nuclear receptor, the receptor undergoes a conformational change, activating the receptor and leading to an increase in gene expression.

An apparent receptor with a structure that is comparable to that of other known receptors but without a known endogenous ligand is known as an orphan receptor. The receptor is referred to as an "adopted orphan" if a ligand for it is later discovered. Instances of vagrant receptors are found in the G protein-coupled receptor (GPCR) and atomic receptor families. Orphan GPCR receptors typically receive the name "GPR" followed by a number, such as "GPR1." Farnesoid X receptor (FXR), liver X receptor (LXR), and peroxisome proliferator-activated receptor (PPAR) are examples of adopted orphan receptors in the nuclear receptor group.

The pharmaceutical industry's development of post-genomic research strategies depends on determining the number of molecular targets that present

an opportunity for therapeutic intervention. It is interesting to consider how many molecular targets this opportunity represents now that we know how big the human genome is. We must be able to comprehend what makes a good drug target 1 from the position that we understand the properties that are necessary for a good drug.

Nuclear hormone receptors (NHRs) and orphan nuclear receptors are two examples of the transcription factors that are included in the nuclear receptor superfamily, which is a group of related but distinct transcription factors. Orphan receptors are so-called because their ligands are unknown, at least at the time the receptor is identified, whereas NHRs are receptors for which hormonal ligands have been identified. Lipophilic hormones, in contrast to hormones for cell surface receptors, can travel through the plasma membrane to the interior of cells, where NHRs transmit signals from glucocorticoids, mineralocorticoids, the sex steroids (estrogen, progesterone, and androgen), thyroid hormones, and vitamin D. The structure of each nuclear receptor is the same.

It should come as no surprise that a thorough understanding of the nuclear receptor superfamily has significant ramifications not only for human biology but also for the research and development of new drug therapies. This is due to the fact that these receptors play a significant role in the etiology of many human diseases and are important therapeutic targets for pharmaceuticals.

A crucial part of drug discovery is predicting how small molecules and proteins will interact with one another. G-protein-coupled receptors (GPCR), enzymes, and ion channels are just a few of the classes of proteins that make up a significant portion of the targets of existing drugs and are important targets for the development of new drugs. As a result, new lead compounds could be discovered with the assistance of knowing and anticipating the interactions between these proteins and small molecules. To address this fourth problem with in silico prediction, a number of methods have already been developed that have proven to be very helpful. Predicting a target's modulators, taking into account each target independently of other proteins, is the traditional model. The usual approaches are ligand-based, structure-based, or docking approaches. Structure-based approaches use the 3D structure of the target to determine how well each candidate binds to the target, whereas ligand-based approaches make their predictions by comparing a candidate ligand to the known ligands of the target, typically using machine learning algorithms.

In order to produce accurate predictors, ligand-based methods require sufficient knowledge of a target's ligands in relation to the complexity of the ligand/non-ligand separation. When a target has few or no known ligands, one must use docking techniques, which take a long time and require the target's 3D structure 6. None of the traditional methods can be used for a target that does not have a 3D structure that can be determined. This is the case for many GPCR because only a small number of crystallized structures have been found, and many of these receptors, which are referred to as orphan GPCR, lack a known ligand.

An intriguing plan to defeat this issue is to quit considering every protein target autonomously from different proteins, and rather take the perspective of chemogenomics. Chemogenomics basically aims to search for interactions between the chemical space, which includes all small molecules, and the biological space, which includes all proteins or at least protein families, particularly drug targets. The realization that certain classes of molecules can bind "similar" proteins is a key motivation for the chemogenomics approach. This suggests that knowing some ligands for a target can help identify ligands for similar

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targets. In addition, this method makes it possible to design drugs in a more rational way because controlling the selectivity profile of a whole ligand is essential for ensuring that there are no side effects and that the compound can be used for therapeutic purposes.

2 MATERIALS

Pubchem: A database of chemical molecules is PubChem. The national center for biotechnology information (NCBI), which is a part of the national library of medicine and is part of the United States National Institutes of Health (NIH), is in charge of maintaining the system. PubChem contains substance depictions and little particles with less than thousand iotas and thousand bonds. This database was used to obtain compounds that were closely related to the particular receptors, namely, after the initial literature review. Ligands.

Marvin Sketch: Marvin Sketch is a chemical structure drawing and visualization package with a molecule drawing tool and integrated chemical file format converter. Marvin consists of Marvin Sketch, Marvin View, a high-performance 3D molecule visualizer, Marvin Space, and Mol Converter, a file format batch-conversion tool. Marvin Space is also a part of Marvin. We mostly used it to reduce energy consumption and convert the formats' chemical files. A single conformation's potential energy can be expressed numerically by summing the energies of various interactions.

This number can be used to evaluate a particular conformation, but because it may be dominated by a few bad interactions, it may not be a useful measurement. A single bad interaction, such as two atoms being too close together in space and possessing a large van der Waals repulsion energy, can cause a large molecule with excellent conformation for nearly all atoms to have a large overall energy. To find the best nearby conformation, it is frequently preferable to perform energy minimization on a conformation. Gradient optimization is typically used for energy minimization: The movement of atoms reduces their net forces. The limited construction has little powers on every iota and hence fills in as a fantastic beginning stage for sub-atomic elements recreations.

PDB: The 3-D structural data of large biological molecules like proteins and nucleic acids are stored in the Protein Data Bank (PDB). The data, which have been submitted by biologists and biochemists from all over the world and typically come from X-ray crystallography or NMR spectroscopy, can be accessed online for free. PDB was used to obtain the receptor IDs and Spdb viewer was used to model the receptors.

HEX: The docking modes of protein and DNA pairs can be calculated and displayed using the interactive molecular graphics program Hex. Hex can also superpose pairs of molecules with just knowledge of their three-dimensional shapes, and it can calculate protein-ligand docking assuming the ligand is rigid. The use of spherical polar Fourier (SPF) correlations to speed up docking calculations is unique to this docking and superposition program.

QUANTUM: The software for QUANTUM docking and library screening screens a compound library against a target protein, calculates the IC50 (Kd, Ki, pKd) value for a protein-ligand complex, and docks a small molecule onto a protein's active site. Instead of using statistical scoring, function-like, and QSAR-like methods, the QUANTUM drug discovery software was developed using a new paradigm in molecular modeling: applying fast quantum and molecular physics. Free binding energy calculations are used in QUANTUM to estimate a protein-ligand complex's binding affinity.

3 METHODS

Collection of Molecules: Literature review was carried out to obtain a list of natural chemo preventive agents targeting

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the receptors. The literature review was carried out from journals like:

a. Pubmed central
b. Oxford journals
c. AACR Journals
d. Nature
e. Springerlink
f. Biomed Central
g. Science Direct etc.

We worked with twenty-three subtypes of fourteen orphan nuclear receptors. It was necessary to locate chemical information regarding the nuclear receptors and ligands. Swiss Prot was used to obtain the receptors' PDB IDs and store the correct receptor crystal structure (Example: 1A6Y.pdb). All of the chemical information about the ligands and receptors was stored in an Excel sheet. This Excel sheet contained drug similarity and information regarding the "Ligand chemical component" for future use.

Creating a Protein Model: The receptors which didn't have their gem structure put away in the protein information bank must be demonstrated utilizing programming called Swiss PDB watcher. This was accomplished by saving the receptor's fasta sequence from NCBI. The blast operation was carried out in order to select the sequence that was the closest to one another and could serve as the "template" (score greater than 200). The template's structure was saved after being downloaded from PDB. The template and the raw sequence (Fasta) were loaded into the software. Tasks like 'Fit crude succession', 'Enchantment fit' were finished and this was submitted. The obtained modeled structure was saved for later use.

3.1 Programming Projects:

Sketch of Marvin: Using a program called "Marvin sketch," all of the ligands underwent energy minimization. A single conformation's potential energy can be expressed numerically by summing the energies of various interactions. This number can be used to evaluate a particular conformation, but because it may be dominated by a few bad interactions, it may not be a useful measurement. A single bad interaction, such as two atoms being too close together in space and possessing a large van der Waals repulsion energy, can cause a large molecule with excellent conformation for nearly all atoms to have a large overall energy. To find the best nearby conformation, it is frequently preferable to perform energy minimization on a conformation. Gradient optimization is typically used for energy minimization: The movement of atoms reduces their net forces. The limited construction has little powers on every iota and hence fills in as a fantastic beginning stage for sub-atomic elements recreations. Also, Marvin Sketch is used to change the file's format so that different programs can use it (from.mrv to.sdf and.pdb).

Database Creation: Macromedia originally developed Adobe Dreamweaver, which was formerly known as Macromedia Dreamweaver. A style sheet language called Cascading Style Sheets (CSS) is used to describe a document's presentation semantics, or how it looks and formats. The most common use for it is to style HTML and XHTML-based web pages. However, the language can also be used to style any XML document, including SVG and XUL. The primary purpose of CSS is to allow for the separation of the layout, colors, and fonts of a document from its content, which is written in HTML or another similar markup language. This separation can make content more accessible, give you more control over how presentation characteristics are specified, let multiple pages share formatting, and make structural content less complicated and repetitive (like by letting you design a website with fewer tables). The most commonly used markup language for web pages is HTML, which stands for HyperText Markup Language. By denoting

the structural semantics of text, such as headings, paragraphs, lists, links, quotes, and other items, it makes it possible to create structured documents. It can be used to create interactive forms and embed images and objects. It is written within the content of the web page using HTML elements that are "tags" enclosed by angle brackets. It can embed scripts that change how HTML web pages behave in languages like JavaScript. HTML can likewise be utilized to incorporate Flowing Templates (CSS) to characterize the appearance and design of text and other material. The W3C, which is in charge of maintaining both the HTML and CSS standards, recommends using CSS rather than explicit presentational markup. Using Dream Weaver, HTML code, CSS templates, and all the chemical information about receptors, ligands, and their interactions, as well as links to other websites, a relational database was created.

4 CONCLUSION

Control of embryonic development, organ physiology, cell differentiation, and homeostasis are all important physiological functions performed by nuclear receptors, a large superfamily of transcription factors. Nuclear receptors have been shown to be involved in numerous pathological processes, including cancer, diabetes, rheumatoid arthritis, asthma, and hormone resistance syndromes, in addition to the normal physiology. As a result, modern biomedical research and drug discovery continue to be very interested in these transcriptional regulators despite their already extensive history. Therefore, it is essential to develop a database capable of combining all of this information about Ligands and Receptors into a package that can provide a scientist or student with relevant information in a timely and precise manner. This is made much easier by creating a database of nuclear receptors and their ligands with information about docking scores, structures, formulas, and other details so that further research can make connections between them, particularly in drug discovery, drug manufacturing, and disease prevention and treatment. Nuclear orphan receptor Databases will soon be the preferred storage option for large multiuser applications that require user coordination. Many electronic mail programs and personal organizers are based on standard database technology, so even individual users find them useful.

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HERBAL DRUGS FOR ASTHMA MANAGEMENT: A CRITICAL REVIEW

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Abstract - Asthma is sickness of the human respiratory framework in which the aviation routes choke and become thin, frequently in light of a "trigger" like openness to an allergen, cold air, practice or profound pressure. It is anticipated that asthma prevalence will rise more rapidly in the coming years as a result of rapid urbanization and industrialization. Although a wide variety of medications are available to treat asthma, their relief is typically symptomatic and short-lived. Additionally, the adverse effects of these medications are quite troubling. Medicinal plants have been used for thousands of years and are widely regarded as a rich source of therapeutic agents for disease prevention. It is undeniable that herbal medicine plays a significant role in asthma treatment. The following are four of the five drug classes that are currently used to treat asthma: Cromones, methylxanthines, 2-agonists, and anticholinergics are herbal remedies that date back at least 5000 years. An attempt has been made to examine antiasthmatic medicinal plants, their active chemical constituent, and a possible mechanism of action in the current article.

Keywords: Bronchodilator, medicinal plants, asthma, and a mast cell stabilizer.

1 INTRODUCTION

The Greek word for "to breathe hard" is the origin of the word "asthma." Through a coordinated global effort, the Global Initiative for Asthma was established to raise asthma awareness among health professionals, public health authorities, and the general public. According to the GINA guidelines' November 2006 final update, bronchial asthma is clearly defined as: a disorder of the airways that causes chronic inflammation and involves numerous cells and cellular components. Wheezing, breathlessness, chest tightness, and coughing are all symptoms of the chronic inflammation, which is linked to airway hyperrespon-siveness. These symptoms typically

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occur at night or early in the morning. Most of the time, these episodes are caused by lung airflow obstruction, which can be widespread or variable, and is usually reversible either by itself or with treatment 1.

According to a number of studies, airway hyper responsiveness plays a significant role in the pathogenesis of asthma, and the degree of airway hyper responsiveness typically correlates with asthma's clinical severity 2. Asthma can be divided into two types based on whether or not there is an underlying immune disorder: a) extrinsic asthma, in which an asthmatic episode is triggered by a type I hypersensitive reaction triggered by exposure to an extrinsic antigen; and b) intrinsic asthma, in which the triggering mechanisms are non-immune and stimuli that have little or no effect on normal subjects can cause bronchospasm 3. It is anticipated that asthma prevalence will rise more rapidly in the coming years as a result of rapid urbanization and industrialization. According to the "Global Burden of Asthma Report," despite the fact that there is a lack of data on the prevalence of asthma in India, the increase is likely to be significant, particularly in India. A wide variety going from 4-19% is accounted for in the commonness of asthma in school-going youngsters from various pieces of India. In Delhi, current-wheezing affects 16.7% of children, with a cumulative prevalence of 20.8 percent.

Asthma's pathophysiology: The pathological infiltration of eosinophils into the submucosa of the airway is a hallmark of bronchial asthma. Eosinophil activation is thought to play a central role in the etiology of this disease by causing damage to the airway epithelium 5 and resulting in the secretion of a variety of highly charged cytotoxic cationic proteins like major basic protein. Acute and chronic inflammation that causes airway narrowing, vascular permeability to increase, edema, and airway smooth muscle contraction are all part of the asthma pathophysiology.

Lung hyperinflation, smooth muscle hypertrophy, lamina reticularis thickening, mucosal edema, epithelial cell sloughing, cilia cell disruption, and mucus gland hypersecretion7 are the gross pathology of asthmatic airways. Patients who passed away from asthma were found to have a significant increase in the thickness of the airway wall throughout the bronchial tree, which was partially caused by smooth muscle hypertrophy 8.

Treatment: Asthma can be treated with any one or a combination of the following medications:

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1. Bronchodilators

- Beta 2 Adrenergic agonists
- Muscarnic antagonists
- Methyl xanthines

2. Anti inflammatory agents

- Glucocorticoids
- Mast cell degranulation blockers (Mast cell stabilizers)

3. Newer drugs

- Leukotriene antagonists
- Anti Ig E antibodies
- Allergy vaccination

2 HERBAL DRUGS USED FOR ASTHMA:

Although numerous medications are available to treat asthma, their relief is typically symptomatic and short-lived. Additionally, the adverse effects of these medications are quite troubling. The worldwide trend has recently shifted from synthetic to herbal medicine, or "Return to Nature." As a rich source of therapeutic agents for the prevention of diseases and ailments, medicinal plants have been known to people for millennia. Numerous medicinal plants have been scientifically demonstrated to have antiasthmatic properties and have been used traditionally to treat asthma.

3 CONCLUSION

Asthma is treated with a lot of synthetic medications, but they are not completely safe to use for a long time. Our nation is endowed with an incredible amount of medicinal plants from nature; As a result, India is frequently referred to as the world's medicinal garden. The significance of herbal medicine in the treatment of asthma cannot be overstated, as evidenced by in-depth scientific studies that have been published in international and Indian journals.

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UNDERSTANDING THE EFFECTS OF PLATELET STORAGE ON OXIDATIVE ALTERATIONS: IMPLICATIONS FOR PLATELET TRANSFUSION THERAPY

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Abstract: Several changes take place during the storage of platelets obtained through apheresis. The purpose of this study was to investigate how storage affected platelet levels of nitric oxide (NO) and glutathione (GSH), protein pattern, activation, and apoptosis. In this study, platelets from healthy donors (n=7) were stored for nine days at 20–24°C in an agitator. Platelets precipitated when the samples were taken on the first, third, fifth, and ninth days, respectively. Annexin-V and a flow cytometer were used to measure platelet apoptosis and platelet activation with PAC-1 and CD62-P antibodies. Spectrophotometry was used to measure the levels of NO, GSH, and malondialdehyte (MDA) in the frozen and thawed platelets. The sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) method was used to investigate the protein pattern of platelets. On the third, fifth, and ninth days, platelet CD62-P, PAC-1 expressions, and Annexin-V levels significantly increased in comparison to the first day. On the same days, platelet NO and GSH levels significantly decreased. Furthermore, only on the fifth and ninth days did MDA levels significantly rise. The density of platelet protein bands changed only slightly. In conclusion, our findings indicate that changes in platelet activity during the storage period may increase platelet procoagulant activity, which raises the risk of trombogenic disease. Therefore, for platelet behavior in vivo, using fresh platelets for transfusion or adjusting platelet preservation are extremely important.
Keywords: Protein, platelet activation, apoptosis, and transfusion.

1 INTRODUCTION

Platelets assume a significant part in keeping up with hemostasis. Since patients with thrombocytopenia require platelet transfusions for treatment, they are frequently used during surgery, chemotherapy, and for bleeding disorders. The preparation of therapeutic platelet concentrates from human donor blood is described using a variety of separation techniques. During prolonged storage, morphology, adhesion and aggregation, membrane features (protein pattern), activation and apoptosis markers, and others may change in platelets obtained through these methods, including apheresis. On the platelet membrane, there are a number of receptors that play a role in adhesion, aggregation (Glycoprotein IIb/IIIa/Fibrinogen receptor), activation (P-selectin), and other cellular processes. Platelet functions may be affected by variations in Gp receptor expression on the platelet membrane as a result of activation signals. In recent years, changes in receptor expression on

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platelets can now be easily detected using fluorescently labelled antibodies. During the storage and preparation of platelet concentrates, it has been demonstrated that platelet GSH levels and expressions of Gp on the platelet membrane shift.

On the other hand, platelet nitric oxide synthase (NOS) has been discovered, and it plays a crucial role in regulating platelet recruitment. In addition, platelet activation and cellular production of O2 radicals, which results in lipid peroxidation, are both increased when platelet NO levels drop. Following the activation of the platelet signaling pathway, lipid peroxidation of membranes caused by reactive oxygen species alters the structure and function of membrane components. In addition, despite the fact that platelets are anucleated cells, events resembling apoptosis occur both in vivo and in vitro. Furthermore, platelets are able to synthesize proteins by utilizing a variety of transport mechanisms and the amino acids that are contained in their cytoplasms. PS (phosphatidylserine) openness is perceived as a marker of cell demise as well just like an enactment marker.

Platelets develop a hypercoagulable environment when exposed to PS on the cell surface for an extended period of time or over a prolonged period of time. The purpose of this study was to investigate how storage affected the levels of NO, GSH, activation, apoptosis, protein pattern, lipid peroxidation, and aphaeresis-derived platelets; In addition, the goal was to determine how any significant changes would affect platelet functions in vivo.

2 MATERIAL AND METHODS

2.1 Materials

Bisacrylamide, bovine serum albumin (BSA), bromophenol blue, coomassie brilliant blue R 250, ethylene diamine tetra-acetic acid (EDTA), hydrogen peroxide (HEPES), glycerin, phosphate-buffered saline (PBS), sodium citrate, reduced glutathione (GSH), Triton X-100, 5-5-dithiobis-2-nitrobenzoic acid (DTNB Lous, MO, USA); Merck (Darmstadt, Germany) supplied methanol, sodium carbonate, ammonium persulfate, TRIS, sodium potassium tartrate, copper sulfate, and thiobarbituric acid (TBA); Becton Dickinson Pharmingen (San Diego, CA, USA) provided the Annexin-V-FITC (Annexin-V-fluorescein isothiocyanate) Apoptosis Detection Kit, binding buffer, and FITC anti-human CD62-P; Becton Dickinson Biosciences, based in San Jose, USA, produced the PAC-1 FITC.

2.2 Subject Criteria

The members of this review are solid intentional blood benefactors who routinely give blood at the Blood Focus of Istanbul College Cerrahpasa Clinical School and have given assent. The participants' ages ranged from 20 to 40. The subjects underwent the standard anamnesis and physical examination. Tests based on serological scanning were used. Ten days before the aphaeresis, the subjects did not take any medication.

2.3 Measurement of GSH

The Mergel et al. method was used to measure GSH levels employing DTNB GSH (2–30 g/ml) served as the standard for the determination of the platelet GSH content. g per 109 platelets was the way the results were expressed.

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2.4 Measurement of Lipid Peroxidation

The precipitate was centrifuged after being solubilized for five hours at 4°C in Tris-NaCl buffer containing one percent Triton X-100 for the purpose of measuring lipid peroxidation. Using spectrophotometry, TBA was used to measure lipid peroxidation in accordance with Buege and Aust's method. The results were presented in the form of nmol/10 mg protein.

3 RESULTS AND DISCUSSION

During surgery and several conditions that cause thrombocytopenia, such as chemotherapy, platelet transfusions are frequently used. Numerous studies have demonstrated that platelets kept in blood bank conditions begin to lose their functions. During storage, platelets undergo a number of changes that make them less useful after a transfusion. Even in the first 24 hours, this loss can be seen in the plasma concentrations. It has been up for debate whether this loss of functions is brought on by the activation of platelets during the preparation and storage process or by changes in the plasma environment's pH and enzyme activation. This phenomenon may be caused by either mechanism.

In this study, we first found that platelet SDS-PAGE bands had a percentage of protein levels determined by densitometry. Platelets have been the subject of several studies to date, and approximately 2,300 proteins have been found in them. Platelet function can be affected in certain ways because of a number of deficiencies and defects in proteins. The loss of signaling proteins is particularly critical to the survival of platelets because signaling proteins initiate significant processes. George NJ and others showed significant glycoprotein misfortune (later this protein is named GPIb) after electrophoresis away platelets. The present investigation looked at the changes that occurred on the membrane protein bands between the first and ninth days. The density of platelet protein bands changed only slightly. However, it should be noted that this study only examined platelet membrane proteins; The alterations in the cytological proteins were not determined by us. In order to demonstrate all of the changes in the protein content, additional studies are required.

Platelet NO levels and oxidative stress parameters were also measured during platelet storage in this study. Strong evidence suggests that oxidative stress plays a role in apoptosis. Additionally, platelet NO and GSH levels significantly decreased on the third, fifth, and ninth days in comparison to the first day in this study; In contrast, MDA levels only increased significantly on the fifth and ninth days (p 0.05). Lipid peroxidation and platelet activation both raise when platelet NO levels drop. Low nitrite levels saw in the review might demonstrate that a few elements are liable for the expansion in platelet enactment, platelet lipid peroxidation and apoptosis. Whether the resulting oxidative changes trigger activation and apoptosis or activation and apoptosis trigger oxidative changes depends on storage is still a complicated phenomenon.

4 CONCLUSION

In conclusion, our findings demonstrate that platelet preparation

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for transfusion increases trombogenic risk in vivo circulation by increasing platelet procoagulant activity and decreasing NO and GSH levels. On the other hand, storage results in defects in the activation properties of platelets, which prevents macrophages from clearing them out. Modern storage techniques will make it easier to make platelets that are ready for transfusion with good haemostatic function and a long time in circulation. In the same way, in vivo conditions, using fresh platelets and adjusting platelet preservation are extremely important for platelet functions.

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EXPLORING SOLID LIPID NANOPARTICLES AS AN EFFICIENT COLLOIDAL CARRIER SYSTEM FOR TARGETED DRUG DELIVERY

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Abstract- Strong lipid nanoparticles (SLN) are watery colloidal scatterings, the framework of which contains strong biodegradable lipids. They were first made available in 1990 as a replacement for conventional colloidal carriers like emulsions, liposomes, and polymeric micro- and nanoparticles. SLN avoids some of the major drawbacks of traditional systems while combining their advantages. They display significant benefits, for example, regulated discharge, further developed bioavailability, insurance of artificially labile particles like retinol, peptides from debasement, savvy excipients, further developed drug fuse and wide application range. The various methods of SLN production, drug incorporation and release, characterization of SLN quality and structure, sterilization, storage, and stability of SLN dispersions, and SLN applications are all covered in this paper.

1 INTRODUCTION

It has become increasingly apparent over the past few years that the creation of novel medications on their own is not sufficient to guarantee progress in drug therapy. The creation of a suitable drug carrier is crucial. Because the carrier system, which should enable a controlled and localized release of the active drug in accordance with the particular requirements of the therapy, now determines the drug's in vivo fate instead of the drug's properties. Solid lipid nanoparticles (SLN) are colloidal carriers that were developed at the start of the 1990s as an alternative to emulsions, liposomes, and polymeric nanoparticles as a particulate carrier system.

Degradation of the polymer in polymeric microparticles may result in systemic toxic effects through impairment of the reticuloendothelial system 2 or accumulation at the injection site; Human macrophages and granulocytes have phagocytosed particles, resulting in cytotoxic effects in vitro3. Additionally, the delivery system may contain organic solvent residues from preparation processes like the solvent evaporation method, which is frequently employed for polyester microparticles and liposomes. These residues have the potential to cause significant issues with acceptability and toxicity. SLNs combine the advantages of other colloidal carriers while avoiding their drawbacks.

They are made of excipients that are well tolerated by the body and can be made on a large scale in an industrial setting through high pressure homogenization, just like emulsions and liposomes. Similar to polymeric nanoparticles, their solid matrix provides the greatest flexibility in the modulation of drug release profiles and protects incorporated active ingredients from chemical degradation. SLN formulations have been developed and thoroughly characterized in vitro and in vivo for a variety of application routes, including parenteral, oral, dermal, ocular, pulmonary, and rectal. An o/w emulsion's liquid lipid (oil) is replaced with a solid lipid or a blend of solid lipids, resulting in SLN. The lipid particle matrix remains solid at both room temperature and body temperature. SLN are made up of 0.1% (w/w) to 30% (w/w) solid lipids that are spread out in an aqueous medium and, if

necessary, stabilized with a surfactant that is preferably between 0.5 and 5% (w/w). It is also possible to incorporate pharmaceutical and cosmetic actives. SLN's average particle size is in the submicron range, between about 40 and 1000nm 5.

1.1 Advantages of SLN:

- Utilization of physiological lipids that biodegrade.
- Avoiding organic solvents that are connected to the method or methods of production.
- Wide range of applications (oral, intravenous, dermal).
- Increased bioavailability of molecules that don't dissolve well in water.
- Intravenous drug delivery at a specific location injection method
- Utilizing dermal application, enhanced drug penetration into the skin and localization in particular skin layers.
- Possibility of cost-effective and relatively straightforward scaling up to the level of industrial production through high-pressure homogenization
- Protection of sensitive molecules and chemically labile agents from the outside environment.

1.2 Disadvantages of SLN:

- The solid lipid's crystalline structure limits its drug loading capacity.
- Modification of the drug's release profile.
- During storage, drug expulsion as a result of the formation of a perfect crystal.
- A growing particle.
- Unpredictable tendency for gelation
- Unexpected polymorphic transition dynamics
- SLN dispersions have a lot of water in them.

General Ingredients of SLN's: Solid lipid nanoparticles are typically prepared with lipids and emulsifiers. Hydrogenated coco-glycerides (Softisan 142), hard fat types (Witepsol W 35, Witepsol H 35, Witepsol H 42, Witepsol E 85), glyceryl monostearate (Imwitor 900), and glyceryl behenate (Compritol 888 ATO) are examples of the lipids that can be degraded and serve as the matrixes in SLN. Cetyl palmitate, glyceryl palmitostearate (Precirol ATO 5), fatty acids (such as stearic, palmitic, decanoic, and behenic acids), and steroid (such as cholesterin) waxes (such as microcrystal paraffin wax and whale ester wax)

Phosphatidylcholine (lecithin, Epikuron 170, Epikuron 200), nonionic wetting agent (e.g., poloxamer 188, 182, 407, 908), cholate (e.g., sodium cholate, sodium glycocholate, sodium taurocholate, deoxy-sodium taurocholate), short-chain spirits (e.g., butanol, butanoic acid), Polysorb Amphipathic materials, such as those of the ionic and nonionic variety, are able to stabilize the dispersion of SLN. On the surface of the SLN, hydrophilic parts stretch to the disperse medium while hydrophobic parts stretch to the core, allowing drug with low water solubility to become entrapped in the SLN and forming the colloidal drug system 8.

2 METHODS OF SLN PREPARATION:

1. **Hot homogenization:** In the hot homogenization method, the active compound-containing lipid melt is dispersed in a hot surfactant solution of the same temperature (five to ten degrees Celsius above the melting point of the solid lipid or lipid blend) by high-speed stirring. The got emulsion (for the most part called pre-emulsion) is then gone through a high strain homogenizer(piston hole homogenizer, MICRON LAB 40) acclimated to a similar temperature by and large applying three cycles at 500 bar or two cycles at 800 bar. The hot O/W nanoemulsion that is made is cooled to room temperature; Solid lipid nanoparticles are produced

when the lipid recrystallizes. Because the lipid phase is less viscous, higher processing temperatures typically result in smaller particles.

2. **Warm homogenization:** Because they would partition between the melted lipid and the water phase during the hot homogenization process, the cold HPH method is ideal for processing both hydrophilic and temperature labile drugs. A cold pre-suspension of micronized lipid particles is produced when the active-containing lipid melt is cooled, the solid lipid is ground into lipid microparticles (approximately 50-100 mm), and the resulting lipid microparticles are dispersed in a cold surfactant solution.
3. **SLN made using the microemulsion method:** Based on the diluting of microemulsions, Gasco and colleagues developed SLN preparation methods 13. Microemulsions, such as o/w microemulsions, are two-phase systems with an inner and outer phase. They are made aby stirring an optically transparent mixture between 65 and 78 degrees Celsius. This mixture typically includes water, an emulsifier like polysorbate 20, polysorbate 60, soy phospha tidylcholine, and taurodeoxycholic acid sodium salt, as well as co-emulsifiers like butanol and sodium monooctylphosphate.

Homogeneous Matrix Model: It comes from lipid and active ingredient solid solutions. When SLNs are made using a cold homogenization method or by avoiding surfactants that could solubilize drugs, a solid solution can be made. The active can be contained in a molecularly dispersed form in a lipid blend. After hardening of this mix, it is ground in its strong state subsequently keeping away from or limiting of the improvement of dynamic particles in various pieces of the lipid nanoparticle. The homogeneous solid solution matrix model is depicted by Etomidate SLN.

Characterization of SLN Quality and Structure: The control of the product's quality necessitates an adequate characterization of the solid lipid nanodispersion. The small size of the particles and the system's complexity, which includes dynamic phenomena, make characterizing SLN difficult. A few boundaries must be viewed as which straightforwardly affect the security and delivery energy:

Measurement of the particle size and zeta potential: Laser diffraction (LD) and photon correlation spectroscopy (PCS) are the most effective methods for routine particle size measurements. Due to difficulties in assessing small nanoparticles and the requirement of electrolytes, which may destabilize colloidal dispersions, the Coulter Counter method is rarely used to measure SLN particle size. Computers (otherwise called dynamic light dispersing) measures the change of the power of the dissipated light which is brought about by molecule development. A few nanometers all the way up to about three microns are covered by this method. This indicates that while PCS can be used to characterize nanoparticles, it cannot detect larger microparticles.

Degree of crystallinity and Lipid Modification: Drug incorporation and release rates are strongly correlated with the degree of lipid crystallinity and lipid modification. Drug incorporation rates decrease while thermodynamic stability and lipid packing density increase in the following order: Super cooled soften < α-alteration < β'- change < β-adjustment. Lipid crystallization and modification changes may be significantly slowed down by the particles' small size and the presence of emulsifiers. The lipid's condition is frequently studied using X-

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ray scattering and differential scanning calorimetry (DSC).

3 INFLUENCE OF INGREDIENTS ON SLN:

- **Influence of the lipid:** Using hot homogenization, it was discovered that as the melting lipid content of SLN dispersions rises, so does the average particle size. On SLN produced by high-shear homogenization 30, the effect of lipid composition on particle size was also confirmed. Witepsol W35 SLN's average particle size was found to be significantly smaller than Dynasan 118 SLN's (175.163.5nm) (117.061.8nm). WitepsolÒW35 contains more limited unsaturated fat chains and significant measures of mono-and diglycerides which have surface dynamic properties. Most of the time, increasing the amount of lipids by more than 5 to 10 percent results in larger particles—including microparticles—and wider distributions of particle sizes. This occurs when particle agglomeration rises in tandem with a decrease in homogenization efficiency.
- **Influence of the emulsifier:** The choice of the emulsifiers and their concentration is of great impact on the quality of the SLN dispersion.
- **Pulmonary administration:** The application of SLN to the delivery of drugs to the lungs has not been sufficiently investigated. Using a Pari-Boy, aqueous SLN dispersions were nebulized, aerosol droplets were collected, and the SLN's size was determined. Particle size distributions of SLN were found to be nearly identical before and after nebulization, with only a small amount of aggregation that was not relevant to pulmonary administration. Dry powder inhalers may make use of SLN powders. Lactose could be used to spray dry SLN.
- **Rectal administration:** According to Sznitowska et al., rectally administered drugs had higher plasma levels and greater therapeutic efficacy than those administered orally or intramuscularly at the same dose. incorporated diazepam into the SLN for use in the rectal area to provide a rapid 60. They discovered that diazepam rectal delivery does not work well with a solid lipid matrix at body temperature. In their subsequent experiments, they decided to use lipids that melt around body temperature. This region appears to be extremely open to examination, particularly when the advantages of rectal course are thought about. PEG coating seems like a promising way to improve bioavailability and delivery through the rectum.

4 CONCLUSION

Due to the successful incorporation of active compounds and the associated benefits, SLN are an appealing colloidal drug carrier system. SLN are a low-cost and easy-to-use medication administration system that can be used in a variety of ways. Covering of SLN with hydrophilic substances is extremely encouraging in the therapy of different illnesses like disease and tuberculosis. They have excellent perspectives that could be developed and successfully promoted. The composition (physiological compounds), the quick and efficient production process, and the possibility of large-scale production are all clear SLN advantages. The promising outcomes of SLN demonstrate their versatility as carrier systems for use in pharmaceutical and cosmetic formulations.

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DIFFERENTIAL PULSE POLAROGRAPHY WAS UTILIZED TO ESTIMATE THE AMOUNT OF TEGASAROD MALEATE

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Abstract - The hydrogen peroxide solution-treated tegaserod maleate can be estimated using a highly sensitive differential pulse polarographic method. The oxidized product at the hanging mercury drop electrode could be quantitatively reduced using differential pulse polarography mode, making the oxidation of tegaserod maleate reversible. The measurement was restricted to 0.1ng/ml. In the presence of 0.1M potassium chloride as the supporting electrolyte, the voltametric peak was located at -1.05 volts. Tegaserod maleate in its tablet form could be successfully analyzed using this method.

Keywords: Hanging mercury drop electrode, differential pulse polarography.

1 INTRODUCTION

Tegaserod maleate (TM), 3,5-methoxy-1H-indole-3-yl-methylene)-N-pentylcarbazimida-mide hydrogen maleate, is a selective partial agonist of the 5-HT4 receptor that has a positive effect on the digestive system. There is no official Pharmacopoeia for the drug. There are a few HPLCMS, HPLC, and spectrophotometric methods for analyzing TM in plasma and formulations, according to a comprehensive literature review. Voltametry provides a collection of highly sensitive and selective techniques. These methods have been used to analyze pharmaceutically relevant compounds in a few reports that are currently available in the literature. After being treated with hydrogen peroxide, the bulk and tablet formulations of TM were analyzed using differential pulse polarography in this study.

A Metrohm 757 Computrace VA voltameter connected to a PC was utilized for voltametric estimations. The multimode anode Metrohm stand was utilized in hanging mercury drop and dropping mercury drop cathode mode. A platinum wire auxillary electrode and a saturated calomel electrode served as the final two components of the three-electrode system. Following the IP procedure, the aqueous 0.1 M potassium chloride was prepared. Water that had been twice distilled

was used to make all of the aqueous solutions.

As a gift sample from the Torrent Research Centre in Ahmedabad, standard tegaserod maleate was utilized without any purification. The local pharmacy supplied the commercial tablet formulation Tegib-6 from Torrent Pharmaceuticals in Ahmedabad, India.

Ten milligrams of standard TM were refluxed for 30 minutes at 80° with 5 ml of 3% H2O2. After being brought to room temperature, the flask was boiled once more for 15 minutes without the reflux condenser to remove the excess H2O2. After cooling, 10 milliliters of methanol were added to the solution. To get rid of any remaining hydrogen peroxide, the solution was boiled for three to four minutes more. The solution was cooled once more and diluted with methanol to 100 milliliters. A stock solution of 1 g/ml was produced by further diluting the solution. Similar preparations were used for other concentrations' standard solutions.

The differential pulse mode was utilized with a pulse amplitude of 50 mV and a drop time of 0.8 s. Twenty milliliters of 0.1 M KCl were taken in the polarographic cell, and nitrogen was purged through the solution for 300 s. An aliquot of 1 l–1 ml from the standard TM solution was then added to the KCl, and nitrogen purging was continued for 10 s. After a 10 s sweep equilibration, the polarogram was recorded. Twenty tablets (Tegib-6 from Torrent Pharmaceuticals) were ground into a fine powder and weighed. 10 mg of powder was weighed, and 5 milliliters of 3% H2O2 were used to treat it as previously mentioned. The standard addition method was used to estimate by adding the standard TM solution at two levels.

We attempted to develop a voltametric method using a glassy carbon electrode after discovering that TM is susceptible to oxidation. However, our attempts to obtain a voltammogram using either the anodic range of DME or the glassy carbon electrode were unsuccessful. However, a sharp polarogram in the cathodic range of a dropping mercury electrode was observed in the TM solution that had already been treated with hydrogen peroxide. As a result, a hanging mercury drop electrode (HMDE) was used to develop the polarographic method in the differential pulse polarographic mode. At -1.05 V, the peak was observed (fig. 1). Various media, including Britton-Robinson buffers (pH 6-12), phosphate buffer (pH range 2-7), and 0.1 M lithium chloride, were tested to see how the composition of the supporting electrolyte affected the shape of the TM polarogram. However, 0.1 M KCl produced the best results, with a polarogram that was sharp

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and clearly defined. The effect of deposition potential on pulse amplitude, voltage step time, and working parameters of differential pulse polarography were investigated with 0.1M KCl as the supporting electrolyte. With a deposition potential of -0.5 V, a deposition time of 68 s, a drop size of 4, an equilibration time of 10 s, a voltage step of 0.006 V, a pulse amplitude of 0.05 s, and a voltage step time of 0.4 s, the optimal parameters are shown in Table 1. Triton-X 100 or any other surfactant was not evaluated because the polarogram was smooth.

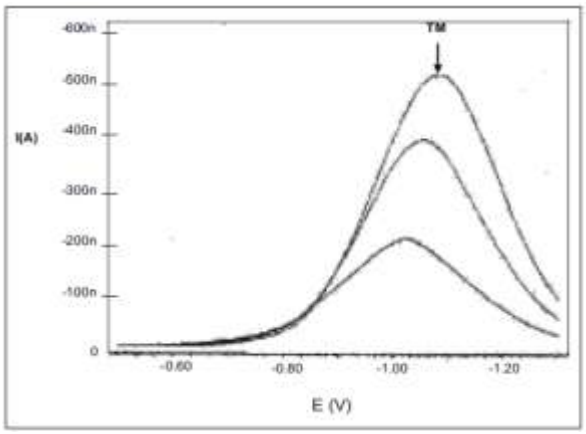

Fig. 1 Differential pulse polarogram of tegaserod maleate The three polarograms are for three different concentrations (0.2, 0.4 and 0.6 µg/ml) of tegaserod maleate solution.

Table 1 Working conditions for differential pulse polarographic analysis of tegaserod maleate

Parameter	Value
Electrode	HMDE
Deposition Potential	-0.5 V
Deposition time	68 s
Drop size	4
Equilibration time	10
Voltage step	0.0060 V
Pulse amplitude	0.05 V
Pulse time	0.05 s
Voltage step time	0.4 s

Six determinations were evaluated for their reproducibility of polarographic response, and the relative standard deviation was found to be 0.56%. The estimated limit of quantification was 0.1 g/l, or 0.1 ng/ml. The standard addition method was used to estimate TM in pharmaceutical preparations using this method (fig. 2). The outcomes showed 100.32±0.68% recuperation recommending results to be in great concurrence with the name guarantee. Although it is an indirect method, the method is

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extremely sensitive and can be used to monitor extremely low TM concentrations.

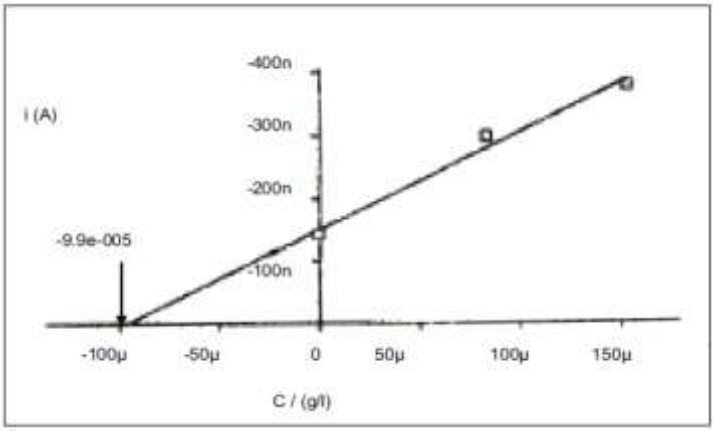

Fig. 2: Analysis of tegaserod maleate by standard addition method The standard addition was done at two levels.

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EXPLORING THE USE OF PLANTAGO OVATA MUCILAGE AS A NATURAL DISINTEGRANT IN FAST DISSOLVING TABLETS: FORMULATION AND CHARACTERIZATION

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Abstract - Prochlorperazine maleate tablets that dissolve quickly were developed in this study to improve patient compliance through direct compression. Microcrystalline cellulose (20-60% w/w) and directly compressible mannitol (Pearlitol SD 200) were used as superdisintegrants in this method, along with Plantago ovata mucilage (2% w/w) and crospovidone (2% w/w) to improve mouthfeel. The hardness, friability, uniformity of the drug content, wetting time, water absorption ratio, and in vitro dispersion time of the prepared batches of tablets were evaluated. The two formulations were tested for drug-excipient interaction (IR spectroscopy), short-term stability (at 40o/75 percent relative humidity for 3 months), and in vitro drug release pattern based on in vitro dispersion time (approximately 8 s). Based on the in vitro drug release characteristics, the formulation made with 8% w/w of Plantago ovata mucilage and 60% w/w of microcrystalline cellulose emerged as the overall best formulation among the two promising formulations (t50% 3.3 min) in comparison to conventional commercial tablets (t50% 17.4 min). The formulations' short-term stability studies showed that neither the drug content nor the in vitro dispersion time changed significantly (p 0.05).
Keywords: Maleate of prochlorperazine, mucilage from Plantago ovata, tablets that dissolve quickly, and crospovidone.

1 INTRODUCTION

Most of the time, mucilage is used as an adjuvant in the production of various pharmaceutical dosage forms. They have binding, dissolving, suspending, emulsifying, and sustaining properties in varying proportions in various pharmaceutical dosage forms, among other pharmaceutical properties. Due to their non-toxic, low cost, free availability, emollient, and non-irritating nature, natural mucilages are preferred to semi-synthetic and synthetic materials. Ispaghula mucilage is made from the dried epidermis of Plantago ovata seeds. Using tablets of prochlorperazine maleate that disintegrate quickly, this study compared the disintegrant properties of Plantago ovata mucilage to those of crospovidone.

Tablets and hard gelatin capsules are difficult to swallow for many patients, leading to noncompliance and ineffective treatment[By developing a convenient dosage form for administration and improving patient compliance, recent advancements in novel drug delivery systems (NDDS) aim to improve drug molecule safety and efficacy. Tablets that break down quickly are one such strategy. A phenothiazine antipsychotic, prochlorperazine maleate (PCZM) is frequently used to prevent and treat nausea and vomiting, including migraine-related or drug-induced emesis. The idea of making tablets that dissolve quickly and contain prochlorperazine maleate is a good and practical way to achieve the

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desired result of faster disintegration and potential increased bioavailability.

2 MATERIALS AND METHODS

Mehta Pharmaceuticals, Mumbai, gave me a sample of prochlorperazine maleate as a gift. A sample of crospovidone came as a gift from the Wockhardt Research Center in Aurangabad. Strides Arcolabs, Bangalore generously donated directly compressible mannitol (Pearlitol SD 200), microcrystalline cellulose (MCC, PH-102), and sodium stearyl fumarate (SSF). The wide range of various synthetics were of logical grade.

2.1 Mucilage is Isolated:

The seeds of Plantago ovata were utilized in the process of isolating mucilage. They were boiled for one hour to release all of the mucilage into the water after being soaked for 48 hours in distilled water. To remove marc, the material was filtered by squeezing it through a muslin cloth. The mucilage was then precipitated by adding an equal amount of acetone to the filtrate. The mucilage was separated, dried in an oven at less than 60 degrees Fahrenheit, powdered (#60 mesh), weighed, and stored in a desiccator until it could be used again.

2.2 How to make tablets of prochlorperazine maleate that dissolve quickly:

Quick deteriorating tablets of prochlorperazine maleate were ready by direct pressure method. Every one of the fixings were gone through #60 cross section independently. Each time, a small amount of both the drug and MCC was taken, blended into a uniform mixture, and the mixture was stored aside. The remaining ingredients were then weighed and mixed geometrically, and a 10-station rotary tablet machine (Clit, Ahmedabad) used 7 mm round flat punches to create 150 mg tablets. For each of the intended formulations, a batch of 60 tablets was prepared.

3 EXAMINING THE TABLETS:

Individually, twenty tablets were selected at random and weighed. To determine the variation in weight, the individual weights were compared to the average weight. Hardness and friability of the not entirely set in stone by utilizing Monsanto Hardness Analyzer and Roche friabilator, separately. Ten tablets were weighed and powdered for the content uniformity test. Methanol was used to extract the powder, which contained 5 mg of PCZM, and the resulting liquid was filtered (Whatman No. 1 filter cloth). After a suitable dilution with methanol, the absorbance at 254.5 nm was measured to determine the amount of PCZM present in the filtrate. The standard calibration curve was used to ascertain the amount of drug. The average of three measurements was used to determine the mean percentage of drug content. A piece of tissue paper that had been folded twice was placed in a small Petri dish that had an internal diameter of 5 cm and contained 6 ml of water to determine the wetting time and water absorption ratio. The time it took to completely wet the paper was measured with a tablet placed on it. The wetted tablet was then gauged. The following equation was used to determine the water absorption ratio (R): R is equal to 100 times (Wa–Wb)/Wa, where Wa is the tablet's weight after water absorption and Wb is its weight before water absorption. One tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffer at 370.5o to determine the in vitro dispersion time. The time required for complete dispersion was then measured. In order to rule out drug-carrier interactions, the KBr pellet method was used to obtain the IR spectra of PCZM and its formulations using a Perkin-Elmer FTIR series (Model 1615) spectrophotometer.

3.1 Study of Dissolution:

In a USP XXIII type-II dissolution apparatus (Electrolab, Model-TDT 06N) with a paddle stirrer at 50 rpm and 900

ml of pH 6.8 phosphate buffer at 37 0.5 o as the dissolution medium, in vitro dissolution of PCZM fast disintegrating tablets was investigated. In each test, a single tablet was used. By measuring the absorbance at 255.5 nm, aliquots of dissolution medium (5 ml) were taken out at predetermined intervals and analyzed for drug content. At each time point, a new volume of dissolution medium was added to the volume that had been taken out. The percentage of PCZM released over time was calculated and plotted.

4 TESTING FOR STABILITY

In order to conduct short-term stability tests on the promising formulations (DPM4 and DCP4), the tablets were kept for three months in an amber-colored rubber stopper vial at 40o/75% RH. The tablets were visually examined for any physical changes, changes in drug content, and changes in the in vitro dispersion time at intervals of one month.

Prochlorperazine maleate tablets were made by direct compression with crospovidone and Plantago ovata mucilage as super-disintegrants in varying proportions and microcrystalline cellulose. To improve mouthfeel, directly compressible mannitol (Pearlitol SD 200) was used as a diluent. Eight formulations were created, along with a DC0 control formulation (without super-disintegrant). Due to uniform die fill and free flowing blends (angle of repose 30o and Carr's index 15%), the tablets that were produced had acceptable variations of less than 7.5%, as required by the IP specification. The drug content was found to be within acceptable limits, between 95 and 101 percent. The tablets were found to have a hardness of about 2.63 kg/cm2. The tablets had a good mechanical resistance because their friability was below 1%. The water absorption ratio and wetting time, which are crucial determinants of the disintegrant's capacity to swell in the presence of little water, were found to be between 11 and 47 seconds and 50 to 86%, respectively. There were two designed formulations out of all of them: DPM4 and DCP4 were found to be promising, and their in vitro dispersion times of 8 to 10 s made it easier for them to disperse more quickly in the mouth.

By and large, the definition DPM4 containing 8% w/w of Plantago ovata adhesive and 60% w/w of microcrystalline cellulose was viewed as promising and has shown an in vitro scattering season of 8 s, wetting season of 11 s and water retention proportion of 86% when contrasted with control detailing (DC0) which shows 244 s, 247 s and half qualities individually for the above boundaries. The results obtained from Plantago ovata mucilage are comparable to and even slightly superior to those obtained from crospovidone, as shown by the experimental data.

In a pH 6.8 phosphate buffer, in vitro dissolution studies were carried out on the promising formulations (DPM4 and DCP4), the control (DC0), and commercial conventional formulations (CCF). percent of the drug that was dissolved in five, ten, and fifteen minutes (D5, D10, and D15), dissolution efficiency at ten minutes (DE10 min), t50 percent, t70 percent, and t90 percent, and the dissolution profiles that were shown. According to these findings, the formulation DPM4 had a 10-minute drug release rate that was nearly four times that of the control formulation and was more than five times faster than that of the commercial conventional tablet formulations of prochlorperazine maleate (t50% 17.4 min).

All of the excipients are compatible with the drug, according to IR spectroscopic studies. All of the typical peaks of pure prochlorperazine maleate were visible in the IR spectra of DPM4 and DCP4, indicating that the drug did not interact with the formulation's components. At the end of the three-month period, the above formulations' short-term stability studies show that there are no significant changes in the

drug content or in vitro dispersion time (p 0.05).

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EXAMINING THE RISKS AND BENEFITS OF DRUG USE DURING PREGNANCY: A CRITICAL ANALYSIS

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Abstract - Pregnancy is an extraordinary physiological condition where drug treatment presents a unique concern in light of the fact that the physiology of pregnancy influences the pharmacokinetics of meds utilized and certain prescriptions can arrive at the baby and hurt. Due to the fact that some women who are pregnant have medical conditions that necessitate ongoing and intermittent treatment (such as asthma, epilepsy, and hypertension), it is not possible to completely avoid pharmacological treatment during pregnancy. This could be harmful. Pregnancy can also bring on new medical issues as well as exacerbate existing ones, such as migraines and headaches, requiring medication. One of the most common issues in medical treatment is the possibility that certain medications administered during pregnancy could be harmful to the unborn child. Phocomalia were born to pregnant women who took thalidomide in the 1960s. There are a number of other known instances of drugs having teratogenic effects. It has been archived that intrinsic irregularities brought about by human teratogenic medications represent under 1% of absolute inborn anomalies. As a result, in 1979, the Food and Drug Administration developed a method that takes into account the quality of data from both animal and human studies to determine a drug's teratogenic risk. The FDA divides various drugs used during pregnancy into five categories: category A is regarded as the safest, while category X is absolutely prohibited during pregnancy. The clinician receives therapeutic direction from this. The various aspects of using drugs while pregnant are the primary focus of this article.
Keywords: Pregnancy physiology, teratogenic drugs, FDA drug classifications, and drug use during pregnancy.

Due to the risk of teratogenic effects and physiologic changes in the mother as a result of pregnancy, drug treatment during pregnancy is especially concerning. Pregnancy's physiology influences the pharmacokinetics of medications, and some medications can harm the fetus. Historical events, such as the thalidomide crisis in the 1960s and the teratogenic effects discovered related to the use of diethylstilboestrol in 1971, have influenced the concern about medication use during pregnancy and lactation. These occasions drove the US Food and Medication Organization to lay out severe guidelines in regards to sedate marking, the utilization of meds in pregnancy, requiring exhibitions of wellbeing and adequacy of any medication before it turns out to be economically available.

1 PHYSIOLOGICAL CHANGES IN PREGNANCY

Pregnancy occurs when a sperm penetrates an egg.

This process, which is known as fertilization, typically occurs in the fallopian tube of the woman. As soon as the egg is fertilized, it begins to divide into a growing collection of cells. The fertilized egg begins to form the placenta between five and seven days after ovulation. By facilitating the transfer of oxygen, carbon

monoxide, amino acids, fats, vitamins, and minerals from the mother's blood, the placenta helps the baby grow and thrive. Additionally, it allows the baby's waste to be transferred. The baby is called an embryo from the time it is inserted into the uterine wall until about the eighth week of its life. During this stage, specialized cells begin to form the vital organs, nervous system, bones, muscles, and blood, accelerating development. A fetus is the developing baby after the eighth week of pregnancy. It is 2.4 centimeters long, has most of its internal organs formed, and starts to develop external features like eyes, nose, mouth, and ears.

Amazing changes in metabolism take place as the fetus and placenta grow and put more pressure on the mother. Weight gain and altered body shape are the physical changes that are most obvious. Breast tissue, blood, and water volume—in the form of extra vascular and extra cellular fluid—all contribute to weight gain. Maternal stores are enhanced by the accumulation of fat and protein as well as an increase in cellular water. During pregnancy, the typical gain in weight is 12.5 kilograms. Protein accounts for 1 kilogram of weight gain during a normal pregnancy. Additionally, there is an increase in fibrinogen and a decrease in plasma albumin levels. Pregnancy causes an increase in total body fat. Plasma lipids rise during the second half of pregnancy, but triglycerides, cholesterol, and lipoproteins fall shortly after birth. During pregnancy, the ratio of LDL to HDL rises.

The dosage and strength of a drug, as well as the fetus's developmental stage, determine how it affects the fetus. The effects of medications during conception and implantation are poorly understood. Women who want to conceive or are at risk of conceiving should stop taking all unnecessary medications three to six months before conception. Early in pregnancy, between 15 and 21 days after fertilization, certain medications may have an all-or-nothing effect during blastogenesis; killing the fetus or having no effect at all The fetus is extremely resistant to birth defects at this early stage. Between the third and eighth weeks after fertilization, the fetus is particularly at risk for birth defects; which corresponds to the organogenesis phase. During this time, the development of all major organs begins. Drugs that reach the fetus at this stage may result in a miscarriage, a birth defect that is obvious, or a defect that is permanent but not obvious until later in life. The embryo is referred to as a fetus at the 9th week. During this time, development primarily consists of growth and maturation. Openness to drugs during this period isn't related with major inborn contortions however they might change the development and capability of ordinarily shaped organs and tissues.

The dose that reaches the fetus also affects how a drug works. The maternal dose, the drug's distribution in the mother's blood stream, placental function, maternal and fetal genetic and physiologic status, and exposure to other drugs, chemicals, or environmental hazards all have an impact on this dose[9].

2 PHARMACOKINETICS IN PREGNANCY

Pregnancy's distinct physiological changes have an effect on the pharmacokinetics of medications that pregnant women take. A woman's plasma volume rises by 30 to 50 percent during pregnancy, and her cardiac output and glomerular filtration rate also rise in a similar way. In a pregnant woman, these factors lower the circulating concentration of some drugs, particularly those excreted by the kidney, possibly resulting in subtherapeutic drug levels. Pregnancy also causes an increase in body fat; which makes fat-soluble drugs more widely distributed. During pregnancy, a decrease in plasma albumin concentration increases the volume of distribution for drugs that are highly protein-bound, such as anticonvulsants.

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However, the kidney and liver excrete the unbound drugs more rapidly; and this mitigates the impact of the increased distribution volume. Gastric emptying time is slowed down by progesterone, particularly in the third trimester, which delays the drug's effects.

During pregnancy, concurrent use of common medications like antacids, iron, and vitamins may also bind and inactivate some drugs. Increased blood flow generally speeds up drug intramuscular absorption; which increases the rate of onset of action and systemic drug absorption. Finally, estrogen and progesterone alter the activity of hepatic enzymes; which can increment drug amassing or decline disposal of some drugs.

3 PLACENTAL TRANSFER OF DRUGS

The uterus; the functional unit of fetal and maternal blood is the product of conception. To keep both the mother and the fetus healthy, the placenta is responsible for nutrition, respiration, metabolism, excretion, and endocrine activity. A drug must diffuse through the placenta from the maternal circulation to the fetal circulation in order to have a teratogenic or pharmacological effect on the fetus. The drug's chemical properties, such as protein binding, pH difference, lipid solubility, and molecular weight, affect the rate of transfer. The placenta is only crossed by free, unbound drug. While fetal albumin rises, maternal plasma albumin decreases during pregnancy. As a result, the free drug's concentration rises as it travels through the placenta to the fetus. Because the pH of the fetus is slightly higher than the pH of the mother, weak bases are more likely to cross the placenta. Drugs that are moderately lipid-soluble can easily cross the placental membrane.

Drugs that have a low molecular weight (less than 500 g/mol) easily spread throughout the placenta. Drugs with a higher sub-atomic weight (between 500-1000 g/mol) cross the placenta less effectively, while a couple of medications with a high sub-atomic weight (>1000 g/mol) don't cross the placental membrane. Due to increased maternal and placental blood flow, decreased thickness, and increased surface area of the placenta, transplacental drug transfer increases in the third trimester.

4 PREGNANCY AND DRUG USE

Drugs are an important tool for boosting well-being and human health. However, they must be safe, effective, and used rationally in order to achieve the desired effect. As a general rule, drugs except if totally fundamental ought not be utilized during pregnancy since drugs taken by a pregnant lady can arrive at the baby and damage it by crossing the placenta, a similar course taken by oxygen and supplements, which are required for the development and improvement of hatchling.

Asthma, epilepsy, and hypertension are just a few of the medical conditions that women with pregnancies may have that necessitate ongoing and intermittent treatment, so avoiding medications while pregnant is not always an option. Pregnancy can also bring on new health issues or worsen existing ones, such as migraine headaches, necessitating medication. The mother's and baby's health may be compromised if these conditions are not managed. Additionally a few medications like nutrients, minerals, iron and dietary enhancements are fundamental for the soundness of pregnant lady and the baby. Due to various chronic diseases and pregnancy-related complications, approximately 8% of pregnant women require drug treatment. Before they realize they are pregnant, many women take medications in the first few weeks. A medicine other than a vitamin or mineral supplement is prescribed to approximately 59% of pregnant women. A dietary herbal supplement is taken by approximately 13% of pregnant women. Prescription or nonprescription (over-the-

counter) drugs, social drugs like tobacco or alcohol, or illicit drugs are used by more than 90% of pregnant women at some point during their pregnancy. One of the traditional issues in medical treatment is the possibility that certain medications administered during pregnancy could be harmful to the unborn child.

Medical trials typically exclude pregnant women, and findings from animal studies need not necessarily apply to humans. As a result, treating pregnant women with certain medications is a challenge, and the majority of doctors take a rather restricted approach to drug use during pregnancy. Clinical research on the safety of drugs during pregnancy has faced numerous obstacles as a result of people's fear of causing harm to the fetus and death. Therefore, case reports, epidemiological studies, and animal studies actually provide information regarding the safety of medications during pregnancy; all of which have limitations, making it difficult to determine the risks of using drugs while pregnant.

5 HOW DRUGS AFFECT THE FETUS

Pregnancy-related medications can have a variety of effects on the unborn child. They have the ability to directly affect the fetus, causing harm or abnormal growth that can result in birth defects or death. Constricting blood vessels and reducing the blood supply of oxygen and nutrients to the fetus from the mother can also alter the function of the placenta, typically resulting in a baby who is underweight and underdeveloped. Additionally, they have the ability to forcefully contract the uterine muscles; reducing the blood supply to the fetus in an indirect way or causing preterm labor and delivery.

6 SOCIAL DRUGS

Other substances that some women use during pregnancy should not be overlooked, in addition to counseling pregnant women about the use of various prescribed and non-prescribed medications. They ought to be made aware of the dangers of using the following substances while pregnant.

7 CONCERNS WITH OTC DRUGS

In India, an increased proportion of drugs are used as self-medications for common complaints and infectious conditions as opposed to prescribed medications due to the easy availability of drugs and inadequate health services. As a result, these customers are constantly at risk for drug reactions and interactions. While many over-the-counter medications can be used during pregnancy with medical supervision, some are known to be dangerous. Before taking over-the-counter medications, women who are pregnant, may become pregnant, or are nursing should consult a doctor, as stated on product labels.

One OTC medication that should be avoided during the last three months of pregnancy is aspirin. Aspirin may cause problems in the unborn child or complications during delivery, so it is especially important not to use it during the final trimester of pregnancy unless specifically instructed to do so by a physician. This warning was issued by the FDA in 1990. Ibuprofen and other over-the-counter non-steroidal antiinflammatory medications carry the same warning about their use during the third trimester.

Experts emphasize that a great deal is unknown about how herbs and nutritional supplements affect a developing fetus in order to determine whether they are safe to use during pregnancy. Therefore, just because a product is available over-the-counter and is marketed as natural, it does not mean that it is safe for use during pregnancy.

8 CONCLUSIONS

Pregnancy's unique physiology makes it difficult to use pharmaceuticals to treat both acute and chronic conditions and to manage a wide range of symptomatic complaints. All clinicians, including

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pharmacists, are obligated to provide patients with complete, accurate, and up-to-date information regarding the risks and benefits of taking medications while pregnant. To effectively counsel women who have been exposed to drugs about the risk of teratogens, exposure must be precisely identified and quantified. This may be simple for prescription drugs, but it may be much more challenging with ethanol or other illegal or over-the-counter drugs. Also, when choosing drugs that can be used safely during pregnancy, drugs that have been used for a long time are often preferred because they have proven safe for the fetus, even if newer alternatives are available.

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REDUCING RISKS IN ASEPTIC PROCESSING: A COMPREHENSIVE REVIEW OF RISK MANAGEMENT STRATEGIES

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Abstract - In the pharmaceutical, biotech, and medical device industries, aseptic processing is a widely used technology for sterile material preparation. In the pharmaceutical industry, the process of putting sterilized parts and products together in a clean, specialized environment is known as aseptic processing. In the pharmaceutical sector, aseptic procedures are among the most challenging to carry out. Aseptically produced sterile products pose a significantly greater risk to the patient than terminally sterilized products due to the nature of aseptic processes. To safeguard the patient, an efficient and high-quality risk management program is required due to the high level of risk. The risk of contamination and the amount of time spent attempting to control insignificant risks are both reduced by an efficient risk management program.
Keywords: Quality risk management, asepticity, validation, risk management, and a risk assessment tool.

1 INTRODUCTION

A product that is sterile does not contain any living organisms, whether they are vegetative or spores. The presence of a single viable organism indicates a failure of the product and the systems (environment, equipment, procedures, and operators) used to produce it. This is an absolute condition, and something cannot be partially or nearly sterile. It is impossible to establish asepsis, the state in which all sterile products that have been aseptically filled are produced. The most difficult manufacturing process is aseptic processing. Operator behavior and training, process validation, production process documentation, maintenance of plant and equipment, and change control management all require careful consideration. According to how they are made, sterile products can be broadly divided into two main categories: those products that are sterilized after the product has been filled and sealed in the final container(s), also known as "terminally sterilized" products, and those products in which the sterilization stage (or stages) occur prior to the bulk product being filled. In this last option example, all ensuing handling (ordinarily, the filling and fixing activities) should be directed aseptically to forestall repeated pollution of the cleaned item.

It is common knowledge that aseptic procedures play a significant role in making formulations that cannot be terminally sterilized sterile. However, due to its increased sterility assurance, terminal sterilization, particularly when carried out with moist heat processes, is regarded as the method of choice for the production of sterile goods. If a manufacturer decides to produce a sterile product without using a terminal sterilizer, they must be ready to demonstrate that the product cannot be terminally sterilized, even with milder autoclave cycles that are tailored to the batch's bioburden (Probability of Survival approach). The two most normal drug utilizations of aseptic handling strategies are (a) the filling of fluid items following cleansing by filtration and (b) the filling of recently disinfected mass powder items 2.

In Pharmaceutical Industries, Aseptic Processing: Aseptic handling is the most

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requesting of drug producing processes. Operator behavior and training, process validation, production process documentation, maintenance of plant and equipment, and change control management all require careful consideration. The health care consumer's safety will always be their top priority for regulators. Due to the risks and potential negative effects it could have on patients receiving health care, aseptic processing is subject to intense regulatory scrutiny. A company's manufacturing license, industry reputation, and financial viability can all be seriously harmed by contamination of an aseptic process. The manufacturer is required by regulatory GMP codes for the aseptic manufacture of human and veterinary products to establish an environmental monitoring program that is appropriately validated to ensure that environmental contaminates are detected in the event of an incident involving product sterility failure or media fill contamination.

Management of Aseptic Processing-Related Risks: In the pharmaceutical sector, aseptic procedures are among the most challenging to carry out. Aseptically produced sterile products pose a significantly greater risk to the patient than terminally sterilized products due to the nature of aseptic processes. To safeguard the patient, an efficient quality risk management program is required due to the high level of risk. The risk of contamination and the amount of time spent attempting to control insignificant risks are both reduced by an efficient risk management program.

Process that is aseptic: In order to produce a sterile product, aseptic processing involves the careful manipulation of sterile components in a controlled environment. While aseptic handling normally includes filling of definite medication item, there are different kinds of aseptic cycles, including aseptic gathering of gadgets or mix items, aseptic crystallization or aseptic precipitation of medication item to deliver a clean mass medication substance, and aseptic plan of conclusive medication item. The high level of risk associated with aseptic processes is one thing they all share. They require extensive environmental monitoring, careful control of the aseptic environment, personnel practices and procedures, sterilization of equipment and components, and numerous other controls. Aseptic processing is one of the pharmaceutical processes with the highest risk due to the large number of controls that must be in place and the severe consequences of control failure. One of the most important tools for ensuring product quality is quality risk management.

Management of quality risks (QRM): Risk is the blend of the likelihood of damage and the seriousness of mischief. Risk to the patient is more important to QRM than risk to other stakeholders like the government, industry, medical professionals, etc. "a systematic process for the assessment, control, communication, and review of risks to the quality of the drug product across the product lifecycle," as defined in ICH Q9, is the definition of quality risk management. This definition emphasizes the fact that quality risk management (QRM) is a systematic process that is intended to manage risks to product quality throughout the product lifecycle. In order to consistently deliver a high-quality product to customers, it is essential to establish a methodical process for managing product quality. The two fundamental principles of quality risk management are outlined in ICH Q9:

- The assessment of quality risk ought to be based on existing scientific knowledge and ultimately linked to patient safety.
- The quality-risk-management procedure's level of formality, effort, and documentation ought to be proportional to the level of risk 4.

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2 THE QUALITY RISK-MANAGEMENT PROCESS: RISK ASSESSMENT

Risk evaluation is the main part of the quality gamble the executives cycle. It entails identifying potential dangers, evaluating those dangers, and assessing the risks associated with exposure to those dangers. The following are some key aspects of the risk assessment procedure:

- A team of qualified experts from engineering, quality assurance, validation, and manufacturing should carry out risk assessments, with assistance from a person who is familiar with the process. The risk question ought to be clearly defined by this team. The risk assessment may lose focus if the risk question is unclear.
- Three central inquiries ought to be responded to in the gamble evaluation: What could go wrong, how likely it is to go wrong, and how bad the consequences will be?
- The "Risk assessment tools" section contains a few of the most common approaches to risk assessment. These devices share a portion of the critical qualities of a gamble evaluation process,
- Precise ID of perils alluding to the gamble question (risk distinguishing proof),
- Assessment of the gamble related with the distinguished danger (risk investigation),
- Correlation of the distinguished and dissected risk against pre-decided measures (risk assessment).

Control of Risk: The creation of a strategy to minimize or accept risks is the foundation of risk control. The reduction of risk to an acceptable level is the goal of risk control. The level of formality and effort required for risk control ought to be appropriate. The accompanying inquiries ought to be posed during this stage: a) Is the level of risk manageable?, b) What measures can we take to eliminate or reduce risks? c) What is the ideal ratio of resources, risks, and benefits? d) Do the efforts to control risk create new risks? The risk control process may produce a risk management strategy. As part of the risk-communication process, this plan may be incorporated into a project plan or validation master plan.

Communication of Risk: Risk communication is simply the exchange of information about risks between decision-makers and other interested parties, either within the company or outside of it. Depending on the product and process's risk level, this can be done formal or informal.

Risk Survey: Risk review is merely a regular examination of risks as part of the ongoing process of quality management. Management reviews on a regular basis, change control programs, and annual product reviews are all instances of formal or informal risk reviews. Risk review ought to be incorporated into the quality-management system in any way that it is carried out.

Tools for Assessing Risk: A partial list of some of the risk assessment tools utilized in the pharmaceutical industry can be found below. This is by no means an exhaustive list. There are various gamble appraisal devices accessible in various ventures and for various capabilities inside a similar industry

Three dimensional gamble Appraisal: A risk assessment tool known as three-dimensional (3-D) risk assessment takes into account a system's distance from the process stream as well as its location along the process stream (for example, API synthesis and purification, bulk product formulation, sterile filtration, filling and stoppering, etc.). and the complexity of the system.

The primary purpose of this tool is to assign a risk level to an entire system. When assessing risks within a pharmaceutical system, additional risk

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assessment tools may be utilized when necessary.

3 ANALYSIS OF FAULT TREES (FTA):

A risk-assessment technique called fault tree analysis (FTA) starts with a failure event and uses logic diagrams to figure out the sequence of events that led to the failure. For critical systems, FTA is frequently used as a design tool. Together with other tools like FMEA, FTA can be used to estimate a failure mode's frequency and ensure that all failure modes are included. Equipment design and commissioning, procedural controls needed to prevent a failure, and qualification and control strategies all benefit greatly from this tool. It can also be used to assign probabilities to each failure mode with some modification. The fact that properly constructing this tool takes a significant amount of time and effort is its only drawback; It can grow quickly as more information is added. Due to the time and effort required, it is better suited for large, complex systems than for simple ones. The following steps are involved in FTA:

- Define the failure (unwanted event) to be studied, gather a team of experts to analyze the system, construct the fault tree, evaluate the fault tree, and create control plans for the hazards that have been identified.

The Effects of Choosing a Risk on Validation: While approving high-risk cycles or exercises, there ought to be proportionately expanded inspecting, testing, or more thorough acknowledgment measures to give more noteworthy confirmation of interaction adequacy. The following risk management principles are specifically incorporated into the FDA process validation draft guidance from 2008:

- Potential variables for DOE studies can be screened using risk analysis tools to reduce the total number of experiments and increase knowledge.
- Utilities and equipment qualification can be covered separately or as part of a project's overall plan.

Risk management can be incorporated into the plan to prioritize particular activities and determine a level of effort required for both the performance and documentation of qualification activities 9. It is necessary to validate any significant modifications to the facilities, equipment, and procedures that may have an impact on the product's quality. "Risk-Assessment Tools:" "The scope and extent of validation should be determined using a risk assessment approach." The frequency and extent of validation are determined using risk assessment tools.

Low-Risk Method: A chilled water framework was utilized to cool a jacketed tank during detailing of an item preceding sterile filtration. This system only makes contact with the tank jacket. A standard temperature control system with a chart recorder was in charge of the chilled water system.

The chilled water system does not require any qualification other than engineering commissioning, making it a low-risk system. The chart recorder and temperature controller were calibrated annually following the system's commissioning under a standard PM program.

Medium-Risk Method: Before sterile filtration, a parenteral product was formulated in a bulk formulation tank. A distributed control system (DCS) was connected to this tank. The DCS uses setpoints entered by the operator from a local panel in the compounding area to control mixing speed and temperature. The operators manually added ingredients other than WFI. The operator from the DCS local panel opened a WFI drop at the mixing tank, which was used to add WFI. The amount of WFI added to the tank is

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indicated by a level transmitter connected to the tank.

High-Risk Method: An injectable protein helpful was not steady in fluid structure and requires lyophilization. The lyophilizer was exceptionally mechanized, with computerized CIP (clean set up) and Taste (disinfection set up), robotized dampness content and item temperature checking utilizing pressure rise technique, and an administrative control and information obtaining framework containing the lyophilization recipes for every measurements type of the item. An autoloading system was used to load the product into the lyophilizer.

The lyophilizer was classified as a system with a high risk score of 125. The lyophilizer's performance was characterized by extensive validation efforts, which included shelf mapping, computerized system validation (CSV), CIP and SIP validation, IQ and OQ, condenser capacity, and sublimation rate, among other tests. Surrogate lots with site-specific sampling for cake appearance, reconstitution, and moisture content were part of the lyophilizer's PQ, followed by media fills and conformance lots for the protein therapeutic. Shelf mapping and periodic requalification of the CIP and SIP processes were included in the change control for the lyophilizer. The lyophilizer was used to fill the media every quarter.

4 CONCLUSION

One of the most important tools for qualifying aseptic processes is quality risk management. It's more than just a CGMP compliance tool; By identifying and controlling critical risks, it adds real value to the validation process. Pharmaceutical companies can ensure that the right resources are used at the right time, at the right place, to improve patient safety and eliminate unnecessary validation efforts by focusing on risk management for the patient.

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EXPLORING THE BENEFITS OF HOLISTIC MEDICINE AS A COMPLEMENTARY APPROACH TO MODERN MEDICINE

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Abstract - The art of living in harmony with nature and caring about the entire universe is known as holistic living. The term "holistic" comes from the idea that a living thing should not be viewed as a collection of various organs but rather as an integrated whole. This is how the term "holistic medicine" got its name. Individuals' physical, spiritual, nutritional, and even social backgrounds are taken into account by the holistic concept. Since mainstream medicine is best suited to crisis intervention and alternative medicine is best suited to health maintenance, holistic medicine is an intelligent combination that utilizes both streams. The term "alternative medicine" refers to a system of health care in which a combination of healthcare systems is used to treat diseases rather than traditional or mainstream medicine. Modern science does not provide the foundation for alternative medical practices, which are based on a belief system. However, holistic medicine does not exclude conventional treatments or incorporate alternative methods. The time has finally come to perceive the arising mindfulness, need and practice of All encompassing and Incorporated medication. Holistic medicine has expanded the range of treatments, making them more efficient, safe, and cost-effective by drawing from a variety of healing traditions from around the world.

1 INTRODUCTION

When seeking treatment for imbalances and making the decision to lead a life that is more balanced, holistic healing refers to adopting a holistic approach. The fact that physical health is not always the primary focus is what sets holistic healing apart from alternative, complementary, and integrative medicine. Correlative and option medicine (CAM) incorporates different recuperating approaches and treatments taken from around the world that generally have not been remembered for traditional Western medication. The indigenous healing systems of China, India, Tibet, Africa, and America are the foundation for many aspects of CAM. A significant number of these medicines and medical services rehearses are well known, and these days even some of them are being utilized in the clinics (for instance, needle therapy and some chiropractic therapies). More and more medical schools are including information about complementary and alternative medicine (CAM) treatments like acupuncture, herbal medicine, chiropractic, and homeopathy as part of their curriculum.

Complementary medicine: Both complementary and alternative medicine (CAM) practices are utilized. Although it is difficult to tell the difference between alternative medicine and conventional medicine, there is a fundamental philosophical difference. Health is typically defined as the absence of disease or dysfunction in conventional medicine. Pathogens, biochemical imbalances, and aging are typical isolated factors that are considered to be the primary causes of disease and dysfunction. Treatment typically entails medication or surgery. In contrast, alternative medicine practices frequently define health holistically, i.e., as a balance of systems that involve the

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entire person, including the physical, emotional, and spiritual. Disease is thought to result from imbalances in these systems. In this instance, treatment entails strengthening the body's own defenses. We want to shed some light on the general aspects and therapeutic benefits of the holistic approach, which is a new trend in modern medicine, in this communication.

Acupuncture: One of the world's oldest forms of treatment is acupuncture; a component of Chinese medicine. It is based on the idea that imbalances in the Yin and Yang forces and disruptions in the flow of Qi cause disease. Practices like spices, contemplation, back rub, and needle therapy look to help mending by reestablishing the yin-yang balance and the progression of qi (energy). Acupuncture3 involves a variety of methods, including the insertion of thin metal needles through the skin, to stimulate specific body points.

Through the stimulation of particular points on the body, it aids in the restoration and maintenance of health and is designed to clear obstructions in the flow of qi. In the US, where specialists consolidate mending customs from China, Japan, Korea, and different nations, needle therapy is viewed as a feature of corresponding and elective medication. The use of acupuncture has been associated with relatively few complications. However, if acupuncture is not administered correctly by a trained practitioner, it may result in potentially serious side effects.

Ayurveda: a medicinal form that originated around 5000 years ago in the Vedic era. "Ayur" refers to life. Ayurveda also suggests treatments for specific mental and physical health issues. The purification of the body of substances that can cause disease is the primary goal of Ayurvedic practices4, and it is believed that doing so will assist in restoring harmony and balance. Ayur implies life while 'Veda' signifies science. As a result, Ayurveda literally translates to "Life Science." It's not just a treatment method; it's also a way of life. The laws of nature, which suggest that life is a combination of the senses, mind, body, and soul, govern the medicinal form. Earth, water, fire, air, and space make up each individual's structural aspect, according to the Science of Life.

In most cases, Ayurvedic medicine aids in the treatment of a specific disease; The mental, emotional, physical, and spiritual well-being are taken into account. The fact that the prescribed doses of medicine are taken in the form of powders, tablets, decoctions, and medicated oils made from natural plants, herbs, and minerals is the best part of receiving an Ayurvedic treatment. Home preparation of the medicines involves traditional methods and processes, while large-scale production necessitates some mechanization. The therapeutics are wonderful because they contain the active ingredients in their natural forms and do not have any side effects when taken as directed.

These include a number of vegetarian diets, such as those followed by macrobiotic advocates and Seventh-Day Adventists. These two groups have significantly lower risk factors for certain types of cancer and heart disease, according to studies. Ongoing investigations have likewise announced that specific social eating styles, like the Asian and Mediterranean weight control plans, seem to bring down risk factors for coronary illness and certain types of disease also. Another diet that has intrigued researchers is the eskimo diet. They are found to be very healthy despite eating a lot of fat. The most recent theory holds that the marine fats they consume, which are high in Omega-3 fatty acids, provide them with this level of protection. Before fungicides were developed, thrush, also known as oral candidiasis, was treated with buttermilk and yogurt. Thrush is a fungus infection of the

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mouth. Scurvy in sailors was treated with fresh limes; Before the "invention" of vitamins, rickets in children were treated with cod liver oil. Warm milk was drank before going to bed for many years to help people sleep. We now know that milk contains an amino acid that makes the brain release a mildly sedative that makes people sleepy.

Reiki: The healing technique known as Reiki11 was developed in Japan. With the intention of facilitating the individual's own healing response, Reiki practitioners place their hands lightly on or just above the person receiving treatment. Reiki is a form of complementary and alternative medicine in the United States. Reiki is used by people to improve their overall health and happiness. People seeking relief from disease-related symptoms and the side effects of conventional medical treatments can also use Reiki. Reiki has been used for self-care for a long time. It is also being provided by medical professionals in a growing number of clinical settings. A lot of scientific research is going on to find out more about how Reiki might work, how it might affect health, and diseases and conditions that it might help with.

Hypnosis: Increased responsiveness to suggestion is a characteristic of hypnosis13, an altered state of consciousness. Relaxing the body is the first step in achieving the hypnotic state, followed by focusing on a select group of ideas or objects as directed by the hypnotist or hypnotherapist. Numerous health conditions, including ulcers, chronic pain, respiratory ailments, stress, and headaches, are treated with the procedure to effect positive changes.

Massage: Massage[14] helps to enhance the function of certain tissues (esp. muscle and connective tissue) and promote relaxation and human well-being.

Meditation: Reflection is a gathering of methods, what began in Eastern strict or profound practices, where an individual figures out how to concentrate and suspend the surge of considerations that regularly consume the human psyche. ' Yoga is a centuries-old practice that aids in the integration of the mind, body, and spirit. The activities of Yoga are planned in such a way to come down on the glandular Frameworks of the body, hence expanding its effectiveness and in this manner, all out wellbeing. It gives the inner cells energy, makes the spinal cord stronger, and makes the nervous system work. It enables us to receive wisdom and knowledge by allowing us to use the body as an instrument for eternal awareness.

2 NATUROPATHY

The term naturopathy, which literally translates to "nature disease," is derived from Greek and Latin words.

- The principle known as Vis medicatrix naturae is at the heart of naturopathy's belief that nature is capable of healing.
- Another belief is that living things, including the human body, are capable of self-healing and maintaining equilibrium.

Instead of using drugs or more invasive procedures, naturopaths prefer to use treatment methods that they believe are the most natural and least invasive. Benedict Lust, who was born in Germany at the end of the 1800s, gave naturopathy its name and made it popular in the United States. Sebastian Kneipp, a German priest and healer, treated Lust when he became seriously ill with tuberculosis. The treatment that Kneipp used was based on a number of popular European healing methods and philosophies, including:

- Hydrotherapy (treatments with water)
- The "nature cure" movement, which advocated returning to nature to regain health. This movement advocated treatments like light

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exercise, herbal medicines, healthy eating, and exposure to the sun and air.

Additionally known as naturopathic medicine, naturopathy a comprehensive medical system that was developed in Europe. Through the use of dietary and lifestyle modifications as well as complementary and alternative medicine (CAM) treatments like massage, joint manipulation, and herbs, naturopathy aims to support the body's ability to heal itself. Supporting health rather than disease prevention is its primary focus. Naturopathic care is sought by people for a variety of health-related reasons, including primary care, wellness support, and the treatment of (mostly chronic) diseases and conditions. Although "natural" treatments are the focus of naturopathy, there are risks associated with it.

Hydrotherapy: The treatment of disease with water is known as hydrotherapy. Aqueous treatment utilizes its temperature impacts, as in hot showers, saunas, wraps, and so on. Numerous cultures, including those of ancient Rome, China, and Japan, have traditionally relied on hydro and hydrothermal therapies to treat illness and injury. Baths were used for healing by the ancient Greeks. Traditional Chinese and Native American healing methods both rely heavily on water. Father Sebastian Kneipp, a monk from Bavaria, contributed to the revival of the therapeutic use of water in the nineteenth century. The mechanical and/or thermal effects of hydrotherapy are the foundation of its recuperative properties.

Homeopathy: The medical system known as homeopathy is based on the idea that any substance that can cause disease or illness in a healthy person can also relieve those symptoms in a sick person. A dose of coffee, for instance, can be given to an insomniac. Managed in weakened structure, homeopathic cures are gotten from numerous regular sources — including plants, metals, and minerals. European homeopathy, also known as homeopathic medicine, is a complete medical system. A method known as "like cures like" is used in homeopathy to encourage the body's natural ability to heal itself by administering extremely low doses of substances that, in larger amounts, would cause illness or symptoms. Homeopathy is used to treat a wide range of illnesses as well as for general health.

Aromatherapy: The term "treatment with scents" refers to aromatherapy. It is a holistic treatment that uses fragrant botanical oils like rose, lemon, lavender, and peppermint to treat the body. The essential oils can be inhaled directly or diffused to spruce up an entire room. They can be added to the bath, massaged into the skin, or inhaled directly. Aromatherapy is used to get rid of pain, take care of the skin, relax, get rid of fatigue, and give the body a new lease on life. The effects of essential oils on mood, energy, anxiety, and relaxation can all be beneficial. They affect the brain and nervous system by stimulating the olfactory nerves when inhaled.

Fundamental oils are fragrant embodiments separated from plants, blossoms, trees, natural products, bark, grasses and seeds with particular helpful, mental, and physiological properties, which improves and forestalls disease. Around 150 essential oils are available. The majority of these oils have disinfectant properties, antiviral, calming, torment alleviating, upper and expectorant. Different properties of the rejuvenating oils which are exploited in fragrance based treatment are their excitement, unwinding, processing improvement, and diuretic properties. Natural raw materials should be used to make essential oils in order to get the most out of them. Oils made synthetically are ineffective.

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Herbal Therapy: Any medical procedure that involves the use of either fresh or dried herbs is referred to as herbal therapy. Supplements, fusions or teas, tinctures, topical creams, and poultices are all ways to use herbs. The creation of a healing steam that is scented with a variety of combinations of herbs may also be part of herb therapy. The history of herbal medicine is still a mystery, but every culture has used herbs to treat a variety of physical and emotional ailments. The healing traditions of China contain perhaps the oldest documented form of this kind of therapy. Chinese herbal therapy is based on the beliefs and principles of Taoism and uses a wide range of herbs to treat illness. In some instances, a single herb is utilized in the therapeutic treatment, while in others, a number of herbs are combined to create a remedy for a specific condition.

Traditional Medicine: Curanderos: In Latin America, Curanderos specialize in using herbal remedies, supernatural forces, and other natural medicines to treat illness. A Curandero is a kind of customary society healer).

Energy healing therapy: In order to restore a normal energy balance and, as a result, health, it involves the practitioner channeling healing energy into the client's body through their hands. It has been utilized to treat a wide assortment of medical conditions, and is much of the time utilized related to other option and ordinary clinical therapies.

Espiritista: An Espiritista is a type of traditional healer who looks at a patient's condition and suggests herbs or religious amulets to help them get better or get over a personal problem.

Feldenkreis: Feldenkreis is a development treatment which uses a technique for schooling in actual coordination and development. Practitioners teach the method in one-on-one lessons and group classes with verbal guidance and light touch. Their primary objective is to improve physical functioning and assist the individual in becoming more aware of how their body moves through space.

Guided imagery: It includes a progression of unwinding strategies followed by the representation of nitty gritty pictures, which are normally quiet and tranquil in nature. The patient will visualize a body free of the particular condition or problem during treatment. Sessions last anywhere from 20 to 30 minutes and are practiced several times per week.

CAM Therapies used the most: Natural products that do not contain minerals or vitamins are the CAM treatment that adults use the most. The practice of pressing, rubbing, and moving muscles and other soft tissues of the body, primarily with the hands and fingers, has increased in popularity for a number of treatments, including deep breathing exercises, meditation, yoga, and massage. The point is to expand the progression of blood and oxygen to the kneaded region.

3 CONCLUSION

The practice of holistic medicine incorporates both conventional and alternative treatments. The art of living in harmony with nature and caring about the entire universe is known as holistic living. As a result, it helps to treat an individual in a unique way that is not only efficient but also quite effective because it takes into account his or her physical, spiritual, nutritional, and even social background. In point of fact, the holistic approach is the one that is needed right now, and people have begun to appreciate its advantages and have begun to focus on this approach, which has begun to gain attention. It won't be long before complementary and alternative medicine (CAM) becomes comparable to any of the current treatment methods.

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