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A REVIEW ON: PATENT LANDSCAPE AND EMERGING THERAPEUTIC FRONTIERS OF PHLOROGLUCINOL-DERIVED BIOACTIVE COMPOUNDS

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ABSTRACT:

Phloroglucinol compounds have attracted significant attention because of their diverse pharmacological activities and broad therapeutic potential. These naturally occurring and synthetic phenolic compounds exhibit antioxidant, antimicrobial, anti-inflammatory, anticancer, antidiabetic, neuroprotective, and gastroprotective properties, making them smedicinal chemistry, biotechnology, and natural product research have accelerated the exploration of phloroglucinol derivatives for the treatment of chronic and infectious diseases. Alongside scientific progress, intellectual property protection has become increasingly important, resulting in a growing number of patents covering novel compounds, extraction methods, synthesis techniques, pharmaceutical formulations, and therapeutic applications. This study reviews the global patent landscape and technological developments related to phloroglucinol-based therapeutics. It examines patent filing trends, leading countries, major applicants, and emerging areas of innovation while highlighting the role of academic institutions and pharmaceutical industries in advancing commercialization. Furthermore, the review discusses recent technological approaches, including green synthesis, nanotechnology-based drug delivery, and computational drug design, that have enhanced the therapeutic potential of phloroglucinol compounds. By integrating scientific literature with patent analysis, this work provides a comprehensive overview of current research progress, identifies existing knowledge gaps, and outlines future opportunities for innovation, collaboration, and the development of safe, effective, and commercially viable phloroglucinol-derived therapeutics worldwide.

KEYWORDS: Phloroglucinol, phloroglucinol compounds, phloroglucinol analogs, phloroglucinols derivatives, natural phloroglucinols, synthetic phloroglucinol.

1.INTRODUCTION: Phloroglucinol compounds represent a broad group of natural, synthetic, and semi-synthetic molecules, with more than 700 naturally occurring derivatives identified to date. These compounds are characterized by the presence of a 1,3,5-trihydroxybenzene core structure, which serves as their fundamental chemical scaffold. Owing to their structural diversity, phloroglucinols have attracted considerable attention because of their wide range of biological and pharmacological properties, including anti-inflammatory, anticancer, antimicrobial, antioxidant, antiallergic, enzyme-inhibitory, and neuroregenerative activities.

Our previous publication provided a detailed review of the naturally occurring classes of phloroglucinol compounds and their biological significance. The current review complements that work by focusing specifically on the technological developments and intellectual property associated with these bioactive molecules. To our knowledge, no earlier review has comprehensively examined the patent landscape or commercialization prospects of phloroglucinol compounds.

The primary objective of this review is to summarize patents related to phloroglucinols, assess their commercial and therapeutic potential, and present an overview of the global technology status of this important class of compounds. A patent search using the keyword "phloroglucinol" identified more than 600 patents. From these, 94 patents with a primary emphasis on pharmaceutical applications were selected for detailed discussion. The review also includes patents describing the isolation and purification of phloroglucinol derivatives with potential therapeutic value. Furthermore, patents associated with compounds highlighted in our earlier review have been incorporated where relevant. Patents covering non-pharmaceutical applications—including cosmetics, pesticides, insecticides, adhesives, textiles, resins, paper products, cement, and polymer industries—are beyond the scope of this review and have therefore been excluded.

Phloroglucinol, either alone or in combination with other compounds, as well as its derivatives, has been utilized as an active ingredient in various pharmaceutical formulations. These formulations exhibit a wide range of therapeutic activities, including antispasmodic, antiviral, antimalarial, vasodilatory, and several other medicinal effects. The different compositions containing phloroglucinol or its derivatives are described in the following sections.

1.1Anti spasmodic composition:

Phloroglucinol is recognized for its antispasmodic activity, and several patented pharmaceutical formulations containing phloroglucinol or its derivatives have been developed for this purpose. Pharmacological studies have confirmed both the safety and therapeutic effectiveness of phloroglucinol. In toxicity evaluations, intraperitoneal administration of doses up to 2 g kg^{-1} in white mice produced no signs of respiratory, cardiac, or convulsive toxicity. Likewise, intravenous toxicity studies in chloral-anesthetized dogs demonstrated no mortality at doses as high as 250 mg kg^{-1}. Long-term toxicity investigations further indicated that phloroglucinol is safe even at doses substantially higher than the therapeutic range and does not exhibit antithyroid activity. Its antispasmodic properties were evaluated using isolated rat duodena obtained from animals fasted for 20 hours and maintained in standard Tyrode solution. Spasms were induced with 10 mg of barium chloride, and treatment with phloroglucinol at doses of 50, 100, and 150 mg effectively inhibited the spasmogenic response in a concentration-dependent manner. Similar protective effects against barium chloride-induced spasms were also observed in the duodenum and ileum of dogs. However, phloroglucinol did not affect acetylcholine-induced contractions in isolated ureters of dogs and guinea pigs, whereas these responses were suppressed by atropine. Clinical studies demonstrated that cachets containing one part phloroglucinol and nine parts glucose were effective as antispasmodic agents. Additionally, phloroglucinol was found to alleviate depression associated with hepatitis and showed therapeutic benefits in the treatment of nephritic colic. Based on these findings, pharmaceutical formulations comprising phloroglucinol combined with sugars such as glucose, lactose, or sucrose have been patented in various dosage forms, including cachets, tablets, capsules, and injectable preparations. [1]

An antispasmodic effect was observed in guinea pigs at a dose of 25 mg/kg. The compound did not alter the effects of acetylcholine or adrenaline, but it exhibited a moderate sedative effect. In addition, Compound 5 demonstrated in vivo antispasmodic activity in guinea pigs when administered intravenously at doses of 10 and 20 mg/kg. It also inhibited contractions of the isolated guinea-pig ureter at concentrations of 20 and 100 µg/mL.

Compound 6 demonstrated a coronary vasodilatory effect in isolated rabbit hearts at a concentration of 100 µg/mL. It also showed antispasmodic activity in guinea-pig ileus *in situ* when administered intraperitoneally or intraduodenally at a dose of 250 mg/kg. In clinical use, Compound 2 has been found to be especially effective in relieving nephritic colic and spasms associated with menstrual disorders. Compound 3 produced highly favorable outcomes in patients suffering from nephritic or hepatic colic. Additionally, Compound 4 proved beneficial in the management of enterocolitis and migraine disorders.

Several antispasmodic therapeutic formulations have been developed from **1-(2-**chloroethoxy)-3,5-dihydroxybenzene, 3,5-di(2-chloroethoxy)phenol.[2], 2-(3,5-dimethoxyphenoxy)ethanol , and 3-(3,5-diethoxyphenoxy)-1,2-propanediol . These patents describe the synthesis of these compounds along with evaluations of their acute toxicity and other pharmacological properties. Compound **7** demonstrated significant antispasmodic activity in isolated rat duodenum, guinea-pig ureter, and ileum preparations. Another patent reported the synthesis and pharmacological assessment of nine derivatives exhibiting antispasmodic, choleretic, tranquilizing, and vasodilatory activities. These compounds include 1-(3′,5′-dimethoxyphenoxy)-2-(N,N-diethylamino)ethane hydrochloride, 1-(3′,5′-dimethoxyphenoxy)-2-morpholinoethane hydrochloride, 1-(3′,5′-diethoxyphenoxy)-2-(N,N-diethylamino)ethane hydrochloride, 1-(3′,5′-diethoxyphenoxy)-2-morpholinoethane hydrochloride, 1-(3′,5′-diethoxyphenoxy)-2-(N,N-diethylamino)ethane iodomethylate, 1-(3′,5′-dimethoxyphenoxy)-2-piperidinoethane hydrochloride, 1-(3′,5′-dimethoxyphenoxy)-2-morpholinoethane iodomethylate, 1-(3′,5′-dimethoxyphenoxy)-2-(N,N-diethylamino)ethane iodomethylate, and 1-(3′,5′-dimethoxyphenoxy)-2-piperidinoethane iodomethylate. Their antispasmodic activity was investigated in vitro using isolated rat duodenum and guinea-pig ureter preparations by measuring relaxation of tissues contracted with barium chloride or acetylcholine. Injectable formulations were prepared for compounds 11 and 13, containing 5–20 mg and 6 mg, respectively, in 5 mL of isotonic sodium chloride solution. Compounds 12 and 14 were formulated as tablets or pastilles containing 100–200 mg and 50 mg of the active ingredient, respectively. These pharmaceutical formulations have been clinically employed in the management of intestinal pain, hepatic colic, and enterocolite colic.

1.2 Antiprotozoal and Antimicrobial compostion :

Natural phloroglucinol-derived compounds have been reported to possess promising anti-malarial properties. Among these are aspidinol , methylene bis-aspidinol, desaspidin, aspidin , flavaspidic acid, and albaspidin . These metabolites exhibited notable anti-plasmodial activity, with methylene bis-aspidinol being particularly potent. It demonstrated IC_{50} values of 325 ng ml^{-1} against the W2 strain and 574 ng ml^{-1} against the D6 strain of *Plasmodium falciparum*. Pharmaceutical formulations have been developed containing 800 ng ml^{-1} methylene bis-aspidinol, 1600 ng ml^{-1} desaspidin, and 1800 ng ml^{-1} aspidin as candidate anti-malarial agents. [3]

Caespitate, another phloroglucinol derivative isolated from the dried aerial parts of *Helichrysum caespititium*, has demonstrated substantial antibacterial and anti-tubercular activities. The compound exhibited minimum inhibitory concentration (MIC) values ranging from 0.5 to 5 µg ml^{-1} against a wide range of Gram-positive bacteria and showed comparable efficacy against common fungal pathogens. Furthermore, it displayed a minimum inhibitory concentration of 0.1 mg ml^{-1} against drug-resistant strains of *Mycobacterium tuberculosis*. Owing to its broad-spectrum antimicrobial potential, caespitate has been incorporated into pharmaceutical formulations intended for the treatment of bacterial, mycobacterial, and fungal infections in humans.[4]

Naturally occurring phloroglucinol derivatives have attracted considerable attention due to their significant anti-malarial potential. These compounds include aspidinol, methylene bis-aspidinol, desaspidin, aspidin, flavaspidic acid, and albaspidin. Among them, methylene bis-aspidinol exhibited the strongest anti-plasmodial activity, with IC_{50} values of 325 ng ml^{-1} against the W2 strain and 574 ng ml^{-1} against the D6 strain of

Plasmodium falciparum. Pharmaceutical compositions containing methylene bis-aspidinol (800 ng ml^{-1}), desaspidin (1600 ng ml^{-1}), and aspidin (1800 ng ml^{-1}) have been proposed as potential therapeutic agents for the management of malaria.[5]

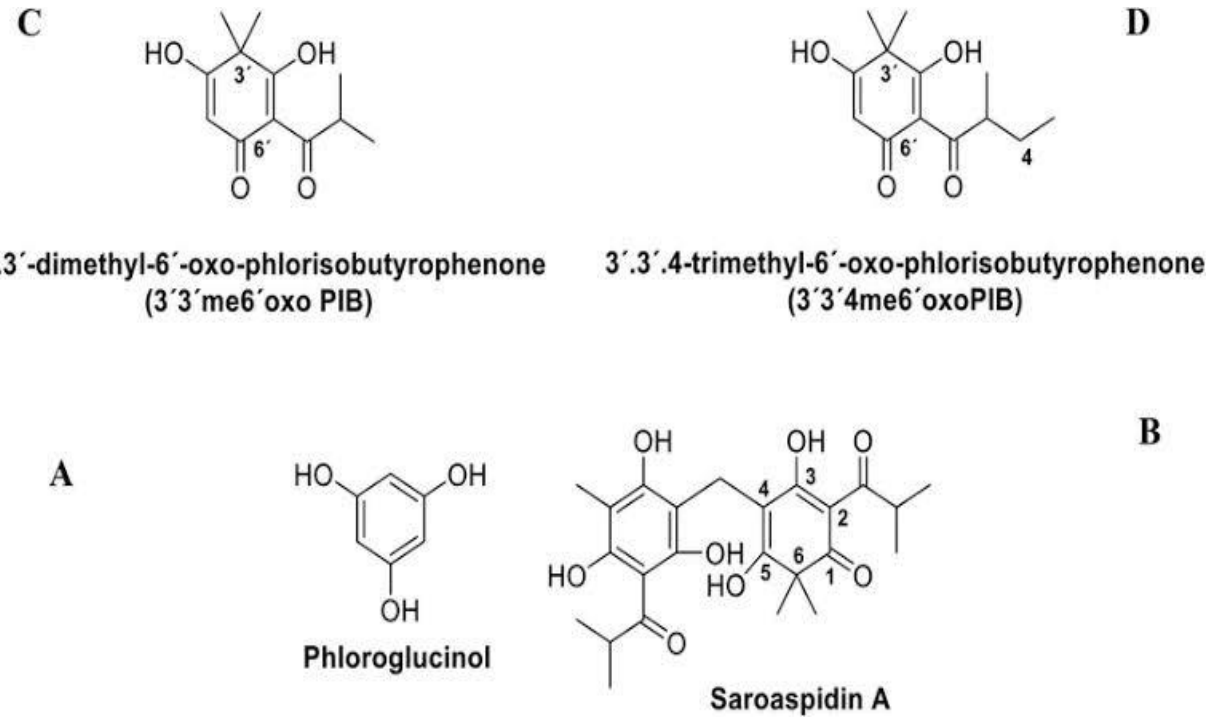
Another phloroglucinol-based metabolite, caespitate , isolated from the dried aerial portions of *Helichrysum caespititium*, has shown remarkable antibacterial and anti-tubercular efficacy. The compound demonstrated minimum inhibitory concentration (MIC) values between 0.5 and 5 µg ml^{-1} against several Gram-positive bacterial species and exhibited similar activity against a variety of fungal pathogens. In addition, caespitate inhibited drug-resistant strains of *Mycobacterium tuberculosis* at a MIC of 0.1 mg ml^{-1}. Due to its broad-spectrum antimicrobial properties, the compound has been incorporated into pharmaceutical formulations designed for the treatment of bacterial, mycobacterial, and fungal infections in humans.[6]

1.3 Anti-viral compostions:

Antiviral formulations containing phloroglucinol or its derivatives, whether synthetically produced or extracted from plant sources, have been reported as active ingredients either alone or in combination with other antiviral agents such as AZT, DDC, and HIV protease inhibitors. The claimed compounds are represented by the general formula, where substituents R1–R6 may consist of hydrogen, alkyl or acyl groups of different chain lengths, aryl groups, halogens, nitro groups, alkylene, alkenylene, and related functionalities. The literature describes synthetic procedures for these compounds as well as methods for their isolation from the leaves of the plant Melicope sessiliflora. In addition, several specific compounds have been identified and characterized for their potential antiviral applications.

The compounds can be administered parenterally, orally, rectally, buccally or transdermally and with a pharmaceutically acceptable carrier or diluent. The compounds can be administered in solid or liquid forms.[7] There are two Japanese patents on anti-herpes virus activity of phloroglucinol compounds. Diacyl phloroglucinol compounds such as 2,4-diacetylphloroglucinol prepared by reacting phloroglucinol with corresponding acid in presence of BF3. Et2O can be used in patients infected with herpes virus. Administration of phloroglucinol compounds can be either oral or by inhalation.[8,9]

chemical structure of phloroglucinol (a) and saroaspidin a (B),



These compounds were obtained from *Ecklonia stolonifera* and demonstrated significant urease inhibitory activity. They have potential applications in the food, pharmaceutical, and chemical industries due to their antioxidant and anti-ageing properties. Additionally, these compounds, whether used individually or in combination, have been patented for their antiviral activity and therapeutic potential.[10]

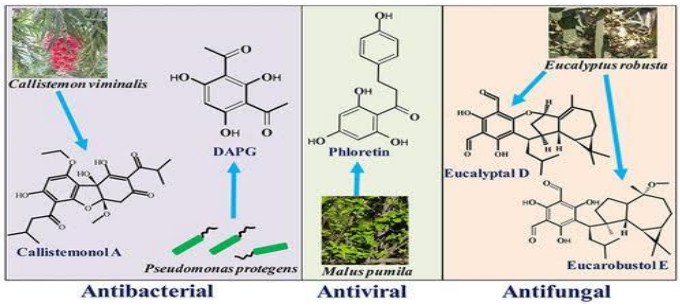
Compounds including humulone, cohumulone , and adhumulone have been incorporated into formulations intended for the treatment of infectious diseases. These formulations exhibit potent activity against methicillin-resistant *Staphylococcus aureus* (MRSA).[11] Additionally, preparations containing these compounds have been reported for their antioxidant properties and their potential use in managing conditions such as rheumatoid arthritis, as well as skin disorders including scalds and acne. Owing to their antioxidant effects, these formulations may also help prevent the deterioration of food and beverage products.[12]Furthermore, mallophenone and its salts have been utilized in formulations designed for the prevention or treatment of ailments such as rheumatism, acne, and various dermal blemishes.[13]

1.4 Dermatological compositions:

A formulation containing 5-methoxypsoralen has been patented for the management of psoriasis and other dermatological disorders. The patent also describes a method for synthesizing 5-methoxypsoralen from phloroglucinol. Generally, furanocoumarins, particularly psoralens, exhibit photodynamic effects when administered either topically or orally and subsequently exposed to ultraviolet (UV) radiation. The therapeutic efficacy of psoralens is known to correlate with their phototoxic properties.

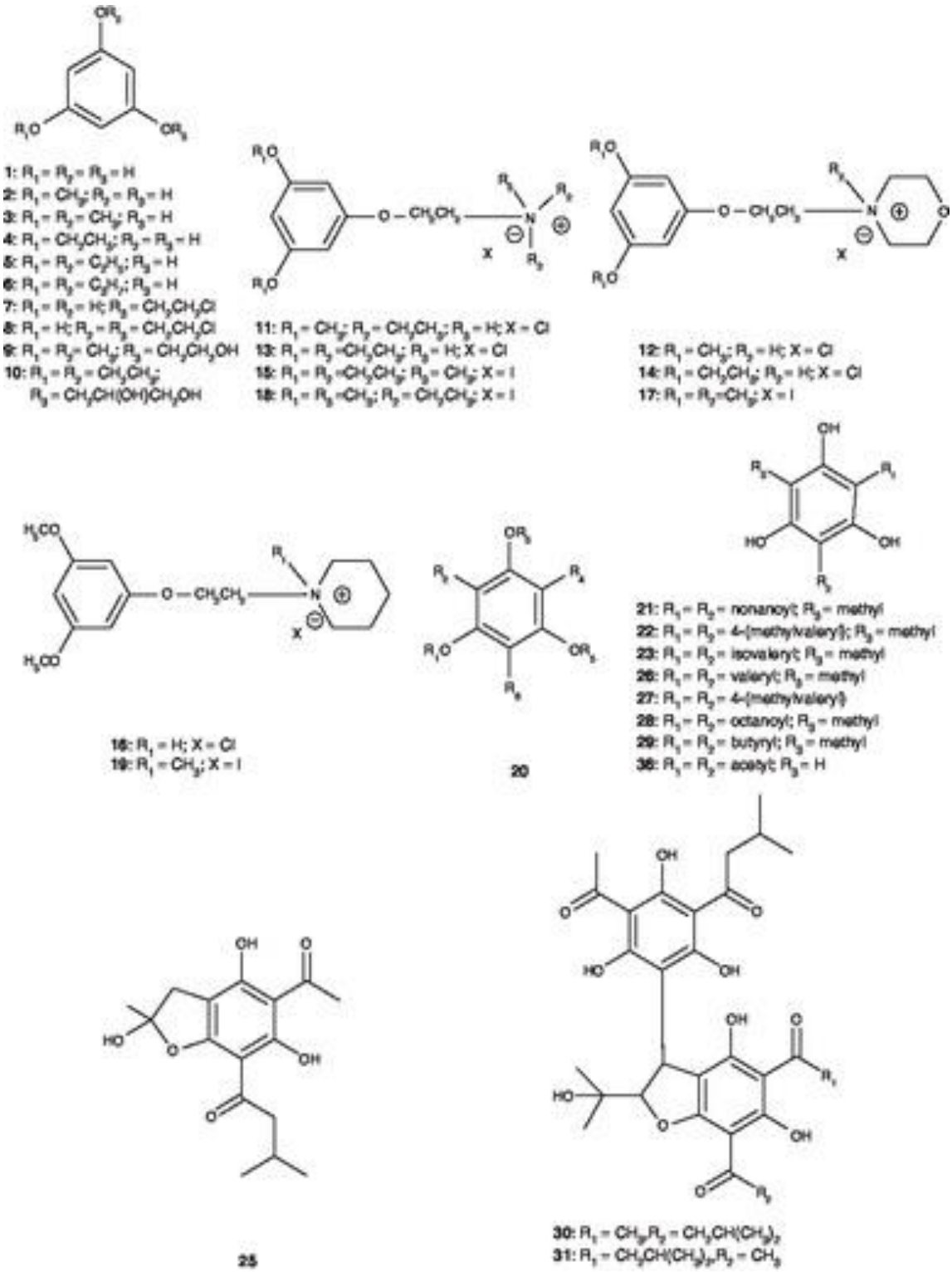
Psoriasis treatment commonly involves oral administration of 8-methoxypsoralen followed by exposure to UV light at 360 nm twice weekly, resulting in significant fading and disappearance of psoriatic lesions. Although compound 58 is less phototoxic and consequently less therapeutically potent than compound 59, it possesses a higher therapeutic index, defined as the ratio of therapeutic activity to acute toxicity, allowing administration at substantially higher doses. Acute toxicity evaluations in male mice and rats revealed that compound 59 was approximately 17 times more toxic than compound 58.

Long-term toxicity studies involving gastric administration of compound 58 to rabbits for 42 consecutive days demonstrated good tolerability. Similar findings were observed following topical application of an oily formulation. Clinical investigations in psoriasis patients showed that oral or topical administration of 58, followed by UV irradiation at 360 nm after 2 hours, produced favorable outcomes. Several case reports documented up to 95% clearance of psoriatic plaques after 20–30 treatment sessions. The compound can be formulated as tablets, oils, aqueous emulsions, or ointments. In some patients, residual lesions remaining after oral therapy responded to local application. The treatment was generally well tolerated, and no recurrence of psoriasis was reported during a six-month follow-up period.[14,15]



Phloroglucinol and Its Derivatives: Antimicrobial Properties toward Microbial Pathogens

Phloroglucinol compounds of therapeutic interest: global patent and technology status:



Diacyl phloroglucinol derivatives possess notable anthelmintic properties. Various C-acylated phloroglucinol compounds have been synthesized, among which 2,4-dibutyrylphloroglucinol, 2,4-diisobutyrylphloroglucinol, and 2,4-divalerylphloroglucinol demonstrated superior activity compared to other derivatives. These compounds can form non-toxic salts with pharmaceutically acceptable strong inorganic or organic bases, making them suitable for incorporation into pharmaceutical formulations. One such derivative, 2,4-di-n-valerylphloroglucinol , was developed as a tablet formulation containing 200 mg of the active compound. The synthesized derivatives showed high selectivity against a range of intestinal helminth

infections in the host. Depending on the severity of the infection, the tablets may be administered to humans between one and six times per day.

1.5 Other pharmaceutical preparations:

Amino ketone derivatives of phloroglucinol and their salts have been utilized as active pharmaceutical ingredients in both conventional and advanced drug delivery systems for managing nerve entrapment and compression disorders. These compounds have been incorporated into oral dosage forms such as tablets, capsules, caplets, syrups, solutions, and suspensions, as well as modern formulations including encapsulated beads, granules, pellets, and transdermal patches. Such preparations demonstrated therapeutic efficacy in nerve injuries resulting from surgical procedures or physical trauma, including conditions such as Kiloh–Nevin syndrome, pseudo-carpal tunnel syndrome, Tardy ulnar palsy, and Guyon's canal syndrome. Compounds such as 4-(pyrrolidinyl)-1-(2,4,6-trimethoxyphenyl)-1-butanone (buflomedil, (2,4,6-trimethoxyphenyl)(3-piperidinopropyl) ketone, (2,4,6-triethoxyphenyl)(3-diethylaminopropyl) ketone , and (2,4,6-triethoxyphenyl)(3-pyrrolidinopropyl) ketone have been formulated into tablets containing 600 mg of the active compound and 450 mg of magnesium oxide, together with suitable pharmaceutical excipients. These agents may also be administered in combination with calcium channel blockers such as felodipine, amlodipine, and nifedipine, as well as α-adrenoreceptor antagonists including cetiedil and ergotamine.[16,17]

Acylated and prenylated phloroglucinol derivatives have additionally been investigated for the treatment of osteoporosis due to their ability to stimulate bone formation and suppress bone resorption. Naturally occurring in *Humulus lupulus* L. (hops), these compounds possess structural similarities to prostaglandin E_2, enabling them to act on osteoblasts and reduce bone loss. α-Acids including humulone , cohumulone , and adhumulone , together with iso-α-acids such as isohumulone, isocohumulone , and isoadhumulone , exhibited potent inhibition of bone resorption at concentrations as low as 1×10^{-9} M in pit formation assays. Pharmaceutical formulations prepared from these compounds include tablets, capsules, granules, powders, enteric-coated tablets, and injectable powders that are reconstituted before administration. The recommended daily dosage ranges from 0.1 to 2.0 g, either as individual compounds or in combination.[18]

The analgesic potential of phloroglucinol derivatives was evaluated using the acetic acid-induced writhing test, in which the number of abdominal contractions following acetic acid administration was recorded. Several compounds demonstrated significant analgesic effects in experimental animals and also exhibited anti-inflammatory activity in the Domenjoz test. Clinical studies involving 15 patients suffering from conditions such as cervicalgia, dorsalgia, and neuralgia of the head and trunk revealed favorable outcomes in 11 patients, with excellent tolerability and therapeutic efficacy. These pharmaceutical preparations can be administered through oral, parenteral, or rectal routes and are available in various dosage forms, including coated tablets, cachets, capsules, injectable ampoules, and oral suspensions.

Phloroglucinol has also found application in antitumor formulations. Preparations containing eriocitrin and/or eriodictyol, together with 3,4-dihydroxycinnamic acid and phloroglucinol, act as apoptosis-inducing agents and are utilized for anticancer purposes. In addition, certain phloroglucinol derivatives possess leukotriene and thromboxane A_2 antagonistic properties. Single-dose formulations containing 1–1000 mg of the active ingredient have been developed as anti-allergic agents.[21] Another derivative, 2,6-diisobutyryl-4,4-diethylcyclohexane-1,3,5-trione, has likewise been employed in anti-allergic drug formulations.[22]

Phloroglucinol-based compounds have also been incorporated into preparations intended to alleviate sexual dysfunction. These formulations typically contain 0.1–50% extracts from marine algae such as *Sargassum fulvellum*, *Ecklonia cava*, *Hizikia fusiforme*, green laver, laver, and *Gracilaria verrucosa*, along with extracts of *Zizyphi fructus*, ginseng, and grape juice. Such compositions are reported to enhance erectile function by promoting longer-lasting erections and stronger ejaculations in individuals with erectile dysfunction.[23]

Furthermore, phloroglucinol β-D-glucoside, known as phlorin, has been utilized in photodynamic therapy for age-related macular degeneration. Formulations comprising phlorin , chlorin, purpurin, and green porphyrin are employed for both the diagnosis and treatment of pathological neovascularization in ocular tissues.[24]

2.0 Patents on compositions containing hyperforin as active ingredient:

More than 40 patents related to hyperforin, a significant phloroglucinol derivative, have been reported. These patents describe various aspects, including extraction techniques, synthetic methodologies, stability properties, and pharmaceutical formulations incorporating hyperforin or its derivatives. Hyperforin, along with its semi-synthetic analogues and naturally derived extracts, has been investigated for use in the prevention and treatment of dementia-related disorders.

2.1Anti-depressant compositions:

Common phytochemicals present in *Hypericum*, including rutin, amentoflavone, and essential oils, contribute to the stabilization of hyperforin within the plant material and its extracts. *Hypericum* biomass may be extracted using supercritical, critical, or near-critical fluids such as carbon dioxide, nitrous oxide, ethylene, ethane, and propane, while methanol, ethanol, or propanol can serve as extraction modifiers. The resulting fractions are biologically standardized by assessing their ability to inhibit serotonin reuptake and are subsequently formulated into hard tablets or soft gelatin capsules. Their stability can be further enhanced through the addition of antioxidants such as tocopherols, whereas bioavailability may be improved using emulsifying agents like lecithin and vegetable oils, including olive oil.[25]

A separate Chinese patent describes the application of *Hypericum* extract in oral pharmaceutical formulations for the management of depression. The preparation, marketed as “Jinyukang,” contains 2–46% hyperforin together with hypericin, pseudohypericin, and flavonoids.[26,27]

Saturated analogs of hyperforin and adhyperforin can be produced by reducing the hexane extract of *Hypericum*. These derivatives may be combined with anti-cholinesterase alkaloids such as galantamine, physostigmine, vincamine, memantine, and tacrine through straightforward methods, including dissolving both components in a common solvent system. The resulting formulations are prepared as hard gelatin capsules or transdermal dosage forms and are intended for the treatment of depression and Alzheimer’s disease.[28]

2.2 Anticancer composition:

Hyperforin has also been reported to be useful in the management of diseases associated with abnormal angiogenesis. Both hyperforin and adhyperforin have demonstrated potential in the treatment of angioproliferative retinopathy, endometriosis, various skin disorders, and diseases affecting bones and joints.[29] In addition, a patent describes the application of *St. John's Wort* extracts for the prevention and treatment of anaphylactic shock and osteoporosis.[30]

Hypericin and hyperforin, together with ginkgolides and flavonoids, exhibit significant antioxidant and antiproliferative properties. Ferrous iron (Fe^{2+}) plays a crucial role in lipid peroxidation, which contributes to oxidative stress. This oxidative damage is associated with several disorders, including Parkinson’s disease, Alzheimer’s disease, Crohn’s disease, ulcerative colitis, and various cancers. Hypericum-derived metabolites, flavonoids, and ginkgolides possess iron-chelating abilities that can be evaluated through ferrous chelation assays. By preventing the formation of iron–ferrozine complexes, these compounds may help manage iron overload and related pathological conditions.[31]

Hyperforin isolated from natural sources can be converted into salt conjugates with amine-containing drugs such as dicyclohexylamine, imipramine, desipramine, memantine, and deprenyl, which are commonly used in the treatment of Alzheimer's disease. HPLC studies demonstrated that these conjugates exhibited greater stability than free hyperforin over a 12-week period. Furthermore, their protein kinase C (PKC) and α-secretase activities remained comparable to those of hyperforin. Approximately 35 such conjugates were developed and formulated into oral, parenteral, and rectal dosage forms. These formulations can be administered at total daily doses ranging from 0.05 to 5 mg/kg body weight, divided into 1–5 unit doses when required.[32]

2.3Miscellaneous compositions of medicinal importance:

Polyhydric phenols, including phloroglucinol and its substituted analogs, are useful in the formulation of blood and plasma replacement products. Traditionally, plasma expanders are produced by partially degrading gelatin that has been pretreated with formaldehyde, which functions as a cross-linking agent to impart desirable colloidal and physiological characteristics. Compounds such as phloroglucinol, resorcinol, and methyl resorcinol enhance and accelerate this cross-linking reaction, thereby facilitating the preparation of plasma substitutes.[33]

Polyhydric phenols also play an important role in the purification of vitamins. Phloroglucinol, orcinol, and hydroquinone are capable of forming stable complexes with cyanocobalamin (vitamin B12), represented by the empirical formula $C_{66}H_{88}N_{14}O_{14}PCo(R)_n(H_2O)_x$, where R denotes a polyhydric phenol and *n* ranges from 4 to 11. In this process, the phenolic compound is introduced into an aqueous vitamin solution, leading to the formation of an insoluble phenol–vitamin complex. The resulting crystals are isolated and subsequently dissolved in water. Highly purified vitamin B12 is then obtained by adding a water-miscible non-solvent to the solution.[34]

3.0 Patents on naturally occurring phloroglucinol molecules with therapeutic activity:

Caespitate , a phloroglucinol derivative with antibacterial and antitubercular properties, was isolated from the aerial parts of *Helichrysum caespititium*. The plant material was extracted by maceration with acetone for 5 minutes to obtain a crude extract, which was subsequently fractionated on a silica gel column using chloroform as the eluent. The collected fractions were screened for antibacterial activity through thin-layer chromatography on silica gel plates impregnated with *Staphylococcus aureus*. Active fractions were further purified by reverse-phase HPLC, and caespitate was detected at 206 nm. Biological evaluation revealed that caespitate was effective against most Gram-positive bacteria but showed no activity against Gram-negative bacteria. It also inhibited the human pathogenic fungi *Aspergillus niger* and *Aspergillus flavus* with a minimum inhibitory concentration (MIC) of 1.0 μg mL^{-1}.[4,35]

Three novel fungicidal compounds were isolated from *Helichrysum decumbens*. Fresh plant material was extracted with chloroform, and the resulting crude extract was separated into flavonoid and phloroglucinol fractions by flash chromatography on kieselgel using a hexane–ethyl acetate gradient. The phloroglucinol-rich fraction was further purified by Sephadex LH-20 chromatography with methanol as the eluent. Fractions of interest were analyzed by HPLC employing a methanol–phosphate buffer mobile phase. Preparative HPLC enabled the isolation of compounds 98–100, which were subsequently evaluated for fungicidal activity. Among them, compound 100 demonstrated activity against *Mucor*, *Cladosporium*, *S. aureus*, and *Bacillus subtilis*.[36]

Garcinielliptone F and Garcinielliptone I were obtained as colorless oils from the fresh seeds of *Garcinia subelliptica*. These compounds were isolated from chloroform extracts through silica gel column chromatography using hexane–ethyl acetate and benzene–ethyl acetate–methanol solvent systems, respectively. Garcinielliptone F exhibited strong enzyme inhibitory activity, whereas Garcinielliptone I

effectively suppressed nitric oxide production.[37] Additionally, 2,4-diacetylphloroglucinol, produced by symbiotic cultures of *Pseudomonas fluorescens*, has been reported to possess both antibacterial and antifungal activities.[38]

Hyperforin may be obtained from plant material through extraction with polar solvents or by employing biphasic extraction techniques. Subsequent purification using acid–base treatment yields an enriched extract containing approximately 65% hyperforin. Further purification through silica gel open-column chromatography followed by high-performance liquid chromatography (HPLC) can produce hyperforin with a purity of up to 95%.[39,40]

A related Chinese patent describes a straightforward, economical, and practical method for the extraction of hyperforin and highlights its potential application as an inhibitor of HIV.[41]

In addition, hyperforin can be recovered from enriched extracts in the form of complexes with mineral salts. Its stability may be enhanced by drying the crude extract at low temperatures while maintaining an appropriate pH range.[42] Selective removal of hypericin from the extracts can also be achieved using polyvinylpyrrolidone, resulting in extracts enriched with hyperforin.[42]

4.0 Conclusions and future perspective:

We examined the available patents related to phloroglucinol compounds, including their applications in different pharmaceutical formulations and methods for their extraction from natural sources. Phloroglucinols appear to be a relatively underinvestigated group of natural products. Based on the patent landscape reviewed, this class of compounds demonstrates considerable promise for the discovery and development of novel therapeutic molecules. Phloroglucinol compounds have found applications across a wide range of therapeutic fields. Internet-based searches indicate that only a limited number of the compounds and herbal products discussed in this review are commercially marketed for medicinal use. Among them, *Hypericum* herb, which contains phloroglucinol derivatives, is the most widely recognized herbal product, with a market value exceeding $1 billion, although estimates vary. Humulex, a commercial preparation containing humulone, isohumulone, and cohumulone, is available as tablets for the relief of mild pain. Psoralens are also important components in the treatment of psoriasis. Phloroglucinol itself is marketed under the trade name Spasfon and is available in tablet form. In France, Spasfon is approved for the management of biliary and urinary tract spasms as well as irritable bowel syndrome. Sales of this analgesic product generated approximately 150 million Euros within just nine months in 2001 for Cephalon, Inc. In addition, it is prescribed for painful menstruation and uterine contractions during pregnancy and is widely employed as an oxidizing and coloring agent in hair dye formulations. Another commercially available phloroglucinol derivative, buflomedil hydrochloride, an aminoketone analogue, is marketed in both tablet and injectable dosage forms.

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