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Review on phytochemical constituents and pharmacological activities of genus *Galium*

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ABSTRACT

Medicinal plants are a rich source of phytochemical constituents of diverse structures that are behind their various pharmacological effects. Plants of genus *Galium* named Bedstraws, family *Rubiaceae*, are distributed throughout North and South America, Europe, the Northern U.S., southern Canada, and tropical Asia. More than 600 species have been used in traditional medicine for treating different ailments. Owing to the valuable published uses of these plant species, and the versatility of their bioactive metabolites such as Galium verum, *Galium aparine, Galium mollugo*, and *G. odoratum*, it was deemed interesting to summarize the previous studies done on this genus to discuss the pharmacological profile of all isolated classes of metabolites. The search was adopted using some essential keywords such as *Galium*, phytochemistry, pharmacology, and biological activity from journals and books in databases such as Scopus, Elton B. Stephens CO, ScienceDirect, Embase, security identifier, and Medline from 1995 to 2024. The results showed that species belonging to *Galium* have various pharmacological activities including antimicrobial, antioxidant, anti-cancer, immunomodulatory, and anti-inflammatory effects because they are rich in phenolic compounds, iridoid glycosides, anthraquinones, phytosterols, saponins, and essential oils. Accordingly, this review will stimulate the scientific community for further research and boost the discovery of novel bioactive compounds from various species belonging to this genus distributed worldwide.

INTRODUCTION

Family Rubiaceae is one of the biggest angiosperm families having a wide number of species distributed worldwide. Its presence in almost all biomes and its diversity make it one of the most valuable components of tropical vegetation [1]. It has been the focus of researchers' attention because of its great pharmacological use being rich in bioactive metabolites including triterpenes, indole alkaloids, iridoids, flavonoids, and anthraquinones [2]. Plants belonging to Family Rubiaceae have been widely used in folk medicine due to their antioxidant, antiviral, antibacterial, anti-inflammatory, and analgesic effects in addition to their activity on the central nervous system and vascular diseases [3]. Moreover their economic importance mainly the Coffea arabica species belonging to the Ixoroideae subfamily rich in caffeine that acts as a vasoconstrictor, central nervous system stimulant, diuretic, bronchodilator, and anti-migraine [4]. As well as the quinine isolated from *Cinchona* species in the Cinchonoideae subfamily by Pelletier and Caventou was for 200 years the only antimalarial drug and is considered responsible for the discovery of synthetic medicines for treating this disease [5]. Other research has isolated bioactive compounds including anthraquinones, iridoid glycosides, flavonols, sterols, and triterpene from *Crucianella maritima* L. (Rubiaceae) growing in Egypt and highlighted the cytotoxic and antimicrobial activities of these isolates [6,7]. The taxonomic classification of the Rubiaceae family is complex and incomplete according to Robbrecht´s classification [8]. The fruits are derived from the bilocular ovary having locules with many ovules. The fruits are of red, orange, blackish, or yellow color and have

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ovoid, spherical, or ellipsoid forms, small in size mainly in Gardenieae belonging to the Ixoroideae subfamily that was subclassified to tribes based on fruit characteristics such as the distinction between berries and drupes [9]. Family Rubiaceae is considered one of the five richest flowering plants having 13,000 species divided into three subfamilies, 620 genera, and 43 tribes. They are found on all continents but are mainly in subtropical and tropical areas. However, the relationships between taxa are not yet resolved since there are indications of polyphyletic/para genera [10]. It is classified into four subfamilies: antirheoideae, rubioideae, ixoroideae, and cinchonoideae. Family Rubiaceae is cosmopolitan, and pantropical with only a few species distributed extra tropically, around half of the species are available in the Neotropics. They are adapted to every habitat even desertic and arid climates. The majority of species belonging to this family are in the Atlantic forests of Brazil, Andean cloud forests, and the Amazon Basin with the endemism centered mainly in the Greater Antilles and the Guyana Highlands in the Neotropics [1].

The genus *Galium* L. is the largest in the tribe Rubieae belonging to the subfamily Rubioideae of family (Rubiaceae Juss.), it has around 600 species, distributed in North and South America, extratropical Eurasia, Australia, Arctic highlands, subtropical to tropical climatic zones, and North America. In Ukraine, about 50 species of Bedstraws are found [11]. This genus is also named yogurt herb because it contains an enzyme giving it the traditional use to coagulate milk [12]. *Galium* L. plants (family Rubiaceae Juss.) are commonly used in folk medicine for treating different ailments mainly infections of the skin, genitourinary systems, and respiratory tract because they are rich in lipophilic complexes of potent antimicrobial activity, mainly against Gram-positive microorganisms and slightly less against Gram-negative bacteria and low toxicity [13]. They are also traditionally choleretic, diuretic, and anti-inflammatory. The most commonly used remedy is the tincture "Tazalok ™" based on *Galium verum* and used for menstrual disorders. Based on the medicinal importance of *Galium* species, and since the previous studies on plants of genus *Galium* have not completely covered all its species regarding their phytochemicals and biological activities, we attempted in this work to summarize and review (1) the phytochemical profile of all plant species belonging to the genus *Galium*, (2) the pharmacological properties of the nutraceuticals isolated from these medicinal plants, (3) the structure-activity relationship between the bioactive compounds´ chemical structure and their mechanism of activity. Accordingly, this review could be of future value regarding the direction of the research on *Galium* species. In addition to the possible discovery of new drugs of various potential activities that serve the pharmaceutical industry.

METHODS

To achieve their work, the authors searched the keywords *Galium*, Rubiaceae, phytochemistry, pharmacology, and biological activity, from 1995 to 2024 from journals and books accessible in databases such as Scopus, Elton B. Stephens CO , ScienceDirect, Embase, Pubmed, and Medline.

RESULTS

Many studies have been successfully conducted on individual *Galium* species, or comparative researches on up to four species were done, to demonstrate the potential of genus *Galium* in treating various diseases. The results collected from all the published articles were reviewed and summarized in our work, and revealed that these plants are rich in phytochemical compounds that are behind their pharmacological activities such as *G. verum* L. named herb Lady`s Bedstraw which is distributed in North Africa, Europe, and Asia, but it can also be found in the northern U.S. and southern Canada. It is a perennial herbaceous plant of the Rubiaceae family rich in phytochemicals such as iridoid glycosides, triterpenes, anthraquinones, phenolic compounds, tannins, essential oils, and saponins. These bioactive compounds provide *G. verum* L a wide application as choleretic, diuretic, and for the treatment of epilepsy and gout [14]. The antioxidant potential of this species was demonstrated by the presence of phenolics mainly gallic acid, flavonoids, and chlorophylls [15]. Moreover, many studies have shown its cytotoxic effect [16], and this activity was tested on colon cancer cells (HT29) and proved that *G. verum* L induces apoptosis and raises the level of Google Scholar in the cancer cells [17]. In addition, *G. verum* L has a protective cardiac activity by preserving the heart's diastolic, and systolic function and cardiac contractility since it alleviates the pro-oxidant production and modulates the antioxidant enzyme activity [18]. The highest level of bioactive compounds and the most potent antioxidant potential is available in the blossoms of *G.verum* mainly due to the presence of iridoids (up to 40.8 ± 2.9 mg AE/g), flavonoids (up to 7.3 ± 0.5 mg QE/g), and polyphenols (up to 27.2 ± 1.5 mg GAE/g). Besides the previous phytochemicals, asperuloside identified in *G. verum* is responsible for the diverse pharmacological effects of the plant mainly anti-hypertensive, anti-inflammatory, and anti-tumorigenic [19]. More studies showed the use of this plant as a diuretic, spasmolytic, choleretic, and in the treatment of hepatitis [14]. Other results supported the medicinal importance of *Galium mollugo* also named false baby's breath, hedge bedstraw, or white lady´s bedstraw, which is distributed in North Africa, Europe, and North America. This species is rich in phytochemicals mainly triterpenes, anthraquinones, phenolics, and iridoid glycosides in addition to other minor compounds such as saponins, tannins, and essential oils. These secondary metabolites make *G. mollugo a* potent antimicrobial mainly against Gram-positive bacteria. Secogalioside is the most important marker of this species and is behind its diverse therapeutic uses as anti-tumorigenic, sedative anti-hypertensive, anti-inflammatory, antibacterial, antiviral, antioxidant, and antifungal [14,20]. Interestingly, the phytochemical investigation of aerial parts of *G. mollugo,* led to the isolation of nine bioactive compounds mainly Z-mollugoside B, mollugoside A, and E-mollugoside B in addition to the following flavonoids including quercetin-3-O-malonyl-glucoside, quercetin-3-O-glucoside, quercetin-3-O-rhamnoside, apigenin-7-O4 glucoside, luteolin-7-O-glucoside, and 2 myricetin-3-O-rhamnoside. These nutraceuticals gave the antioxidant potential to *G. mollugo* since some of them showed significant inhibition of Google Scholar production in fibroblasts exposed to AAPH (2,2'-Azobis(2-amidinopropane)

dihydrochloride) [21]. Another valuable *Galium* species is *Galium odoratum,* which was recognized for centuries for treating various ailments mainly microbial infections as tea or dry extract, it was also applied topically for external wounds in traditional medicine and as anti-hypoxic and antimicrobial, and also to improve memory and metabolism, digestive and liver problems, stomach complaints, central nervous system problems and disorders, jaundice, and gout treatment [22]. The pharmacological potential is due to the versatile nutraceuticals mainly polyphenolic compounds such as coumarin, asperuloside, rutin, quercetin, monotropein, scandoside, and kaempferol in addition to around 96 compounds in the essential oil mainly thymol (30.6%) and isothymol (22.8%) [23]. *G. odoratum* is used for urinary, and stomach disorders and as a spasmolytic, expectorant, and against liver and bile diseases [24]. The antioxidant potential of essential oils has gained the interest of the medicinal industry and researchers, and many studies have been done to investigate their protective effect among which the study that showed the effect of *G. odoratum* in reducing the damage of DNA caused by oxidation in cultured human lymphocytes [25]. Its antimicrobial, antiviral, and antifungal activities were documented and proved that its ethanolic extract has an antimicrobial inhibition zone comparable to that of Gentamicin mainly against Gram-positive bacteria. Another proven effect is the locomotor activity decreasing potential in a dose-dependent manner giving this plant species a significant sedative effect acting on the central nervous system without affecting the muscle tone and coordination [26]. Interestingly, *Galium aparine* L. (catchweed bedstraw) which is native to North America and Eurasia, is widely spread among the *Galium* genus, is included in the British Herbal Pharmacopoeia, and is also named «goosegrass» or cleavers. It is traditionally used for treating many skin ailments and burns in tincture form in different antihomotoxic remedies due to the presence of phytochemicals such as iridoids, polyphenols, and flavonoids mainly quercetin 3-O-rhamnoglucoside-7-O-glucoside [27,28]. The antidiabetic and antioxidant properties of *G. aparine* have been demonstrated in several studies on seed extracts [29]. Several reports revealed that methanolic extracts of this species have anti-cancer effects by targeting the cancer cells only without affecting the normal cells as shown in the study done on breast cancer cells and the result was killing the apoptosis-resistant cancer cells by *G. aparine* plant [30]. Moreover, other bioactive substances were isolated from the roots and rhizome of this plant such as coumarins and anthracene compounds mainly alizarin in the roots responsible for the antifungal and antibacterial activity in addition to the isolation of sesquiterpenoids and fatty acids [31]. Other studies confirmed the use of this plant as antimicrobial, antioxidant, and immunomodulatory due to the presence of flavonoids, polyphenols, and hydroxycinnamic derivatives [27]. *Galium* species information collected in Tables 1 and 2 show their distribution, and phytochemical profile in addition to the diversity of their secondary metabolites' chemical structure and their biological activities.

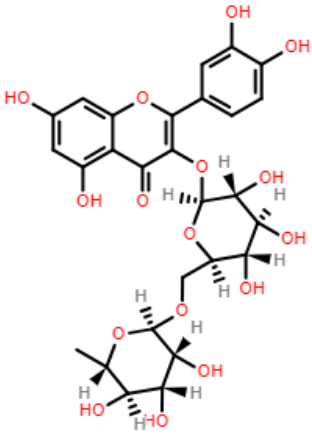
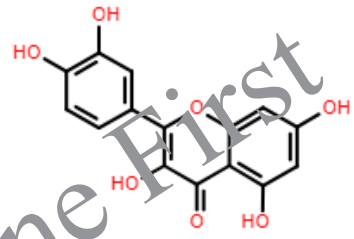
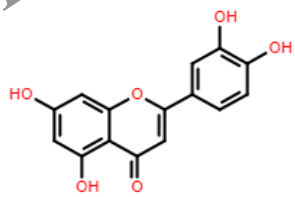
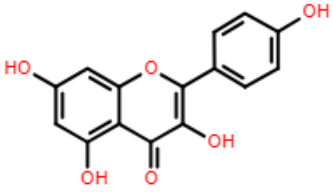
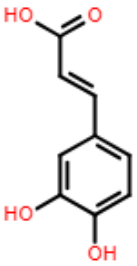
Table1. *Galium* species´ distribution worldwide.

Galium species	English name	Distribution	Ref.
G. verum	Lady`s Bedstraw	North Africa, Europe, and Asia, but it can also be found in the northern U.S. and southern Canada	[14]
G. mollugo	Hedge bedstraw or false baby's breath	North Africa, Europe and North America	[20]
G. aparine	Catchweed bedstraw or cleavers	North America and Eurasia	[27]
G. odoratum	Sweet woodruff	Siberia, Northern and Central Europe, Northern Africa and various regions in the north of Iran	[46]
G. rivale	River bedstraw	Europe to Siberia and Palestine	[34]
G. palustre	Marsh-bedstraw	The Mediterranean area and Western Europe, it has become naturalized in North America and other parts of Europe	[47]
G. tinctorium	Stiff marsh bedstraw	Eastern part of North America, from Texas to Labrador and from Minnesota to Florida, plus eastern and central Mexico and the Dominican Republic	[48]
G. boreale	Northern bedstraw	Northern and central Europe, including Britain, south and west to N. Italy and W. Asia.	[49]
G. spurium	Stickwilly or false cleavers	Europe except the north, western Asia, southern tip of Vancouver Island, across the prairie provinces, and in southwest Ontario and southwest Quebec	[50]

DISCUSSION

The literature review showed that *Galium* species have wide biological activity and this potential is due to the presence of phytochemicals of versatile structure. But despite the successful use of *Galium* plants in traditional medicine for the treatment of various ailments for centuries, the number of studies referring to their pharmacological potential is limited. A comprehensive study of the pharmacological activities of *G. verum* and *Galium mollugo* has been discussed by Bradic *et al*. (2021) to highlight their diverse potential including anti-cancer effects, besides their effects on central nervous system, hepatobiliary, renal, gastrointestinal, and urinary system, in addition to their antioxidant, antifungal, and antibacterial activities [14]. More published articles revealed that the antioxidant potential of *G. verum*, *G. palustre*, *G. cruciata*, and *G. divaricatum* was related to the high level of flavonoids and phenolics [32]. Interestingly, the broad pharmacological potential of *G. odoratum* is due to the high concentrations of coumarin making that species a commercially grown plant to produce coumarins, since this phytochemical is antitumor, bacteriostatic, antipsoriasis, cytotoxic, hepatoprotective, analgesic, antipyretic, and anti-cancerous. Moreover, coumarin is used in the development of many therapeutic drugs used as anticoagulants [26]. Interestingly, Secogalioside

Table 2. Chemical structure of the phytochemicals isolated from various *Galium* species [14–16,18,19,23,28,31,33,38,39–47].

Phytochemicals isolated from Galium species	Chemical structure	Biological activity
Phenolic compounds (from the aerial parts of the plant species)		
Rutin (*G.verum* blossoms) (*G. mollugo*)		antioxidant, anticancer, antifungal, antibacterial
Quercetin (*G.verum,G. mollugo, G. aparine*)		
Luteolin (*G. mollugo, G. verum*)		
Kaempferol (*G. mollugo, G. verum*)		
Caffeic acid (*G. mollugo, G. verum, G. aparine, G odoratum*)		

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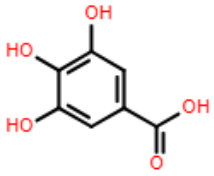
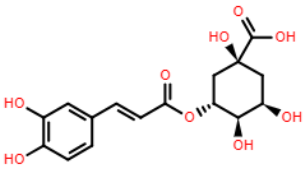
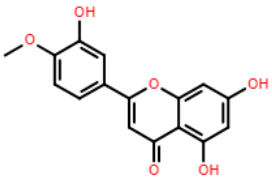
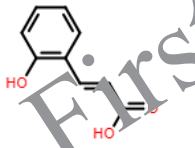
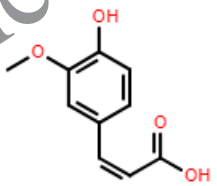
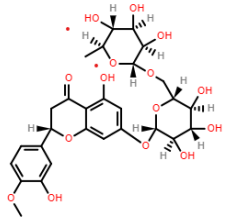
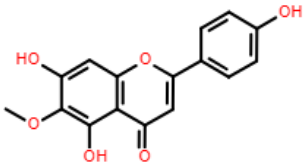
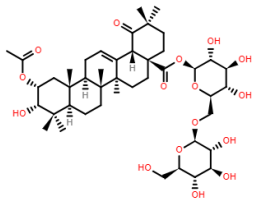
Phytochemicals isolated from Galium species	Chemical structure	Biological activity
Gallic acid (*G. mollugo, G. verum, G.cruciata*)		
Chlorogenic acid (*G. mollugo, G. verum, G. aparine, G odoratum, G. album*)		
Diosmetin *(G. mollugo, G. verum)*		
Coumaric acid *(G. mollugo, G. verum*)		
Ferulic acid *(G. mollugo, G. verum*)		
Hesperidin *(G. mollugo, G. verum*)		
Hispidulin *(G. mollugo, G. verum*)		
Triterpene Saponins (from the aerial parts of the plant species)		
Rivaloside A (*G. rivale*)		Antifungal, antioxidant, antineoplastic, antiviral, antibacterial

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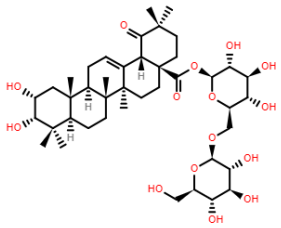
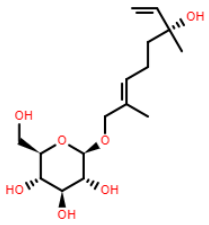
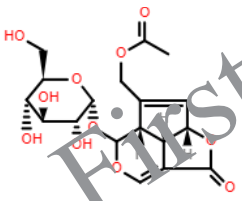
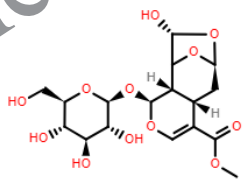
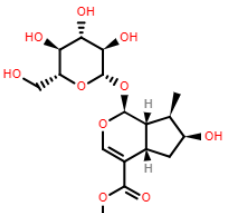
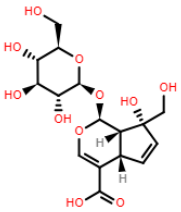
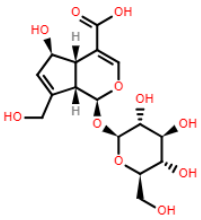
Phytochemicals isolated from Galium species	Chemical structure	Biological activity
Rivaloside B (*G. rivale*)		
Betulalbuside A (*Galium verum*)		
Iridoid glycosides (from the aerial parts of the plant species)		
Asperuloside (*G. verum blossoms, G. aparine)*		Anti-tumorigenic, sedative anti-hypertensive, anti-inflammatory , antibacterial , antiviral, antioxidant, antifungal
Secogalioside (*G. mollugo, G. verum*)		
Loganin (*G. mollugo, G. verum*)		
Monotropein (*G. mollugo, G. verum, G. odoratum, G. aparine*)		
Scandoside (*G. mollugo, G. verum, G. odoratum*)		

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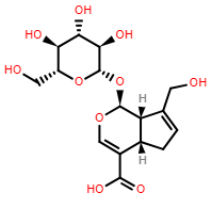
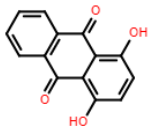
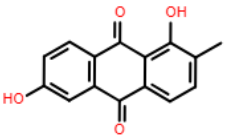
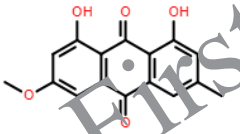
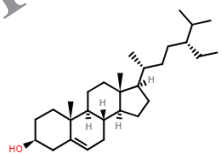
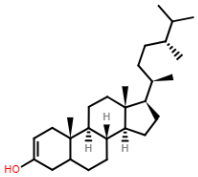
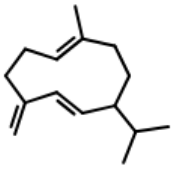
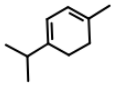
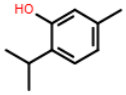
Phytochemicals isolated from Galium species	Chemical structure	Biological activity
Geniposidic acid (*G. mollugo, G. verum*)		
Anthraquinones (from the roots of the plant species)		
Quinizarin (Roots of *Galium.sinaicum*)		
Soranjidiol (Roots of *G. sinaicum*)		
Physcion (*G. verum)*		
Phytosterols (from the aerial parts of the plant species)		
β-sitosterol (G. *mollugo, G. verum, G. odoratum, G. aparine*)		Anti-hypertensive, anti-inflammatory, anti-tumorigenic and antioxidant
Campesterol (*G. mollugo, G. verum, G. odoratum, G. aparine*)		
Essentiel oils (from the aerial parts of the plant species)		
Germacrene D (*G. verum*)		Antioxidant, antibacterial,antifungal, skin disorders, effects on renal, hepatobiliary, gastrointestinal and urinary system
Terpinene (*G. verum*)		
Thymol (*G.odoratum, G. aladaghense, G .incanum, and G. dieckii*)		

being the major component in *G. mollugo* is responsible for the biological activities of this plant mainly its anti-tumorigenic, sedative, anti-hypertensive, antioxidant, and antimicrobial [20].

The structure-activity relationship studies showed that flavonoids found in most *Galium* plants have a specific mechanism of action based on increasing intracellular mitochondrial Google Scholar, damaging cellular DNA, and this is related to the effect of *G. verum* on human fibroblast cells which is increasing apoptosis induction [16]. However, the chemical structure of flavonoids relies on the number and position of hydroxy groups on the B ring in addition to the position of the catechol b-ring that influences the biological activity mainly the potency of its antioxidant potential [33]. Other authors noticed that polyphenols work as scavengers of free radicals, regulators of nitric oxide, and hence inhibitors of cell proliferation, and these various mechanisms are behind the preventive effects of *Galium* plants including antioxidant, neurodegenerative, cardiovascular, and anti-cancer. For example, the tea of *G.verum* is recommended in the treatment of larynx and tongue cancer and in decoction form, it was shown beneficial in head, neck, breast, and oral cancer. Besides all the previous nutraceuticals in *Galium* plants, *G. mollugo, G. verum, G. odoratum,* and *G. aparine* being rich in phytosterols have anti-cancer activity mainly against colon cancer because it was reported that phytosterols induce apoptosis by targeting several signaling pathways [41]. Interestingly, phytosterols act as antitumors by boosting cancer immune recognition, affecting the growth of endocrine tumors that are hormonal-dependent, and altering the biosynthesis of sterols. Besides, these phytoconstituents act by direct inhibition of tumor growth and metastasis, slowing the progression of the cell cycle [42]. Accordingly, since studies have shown that the dietary intake of stigmasterol and β-sitosterol resulted in a decrease in ovarian and esophageal cancer risks, respectively [43], it would be interesting to undergo anticancer studies on *G. mollugo, G. verum, G. odoratum,* and *G. aparine*, being rich in phytosterols. It was demonstrated that the ethanolic extract of *G.verum* rich in phenolic compounds acts by inducing apoptosis and cell death and this mechanism leads to inhibition of human breast cancer cell proliferation [14]. Concerning the immunomodulatory potential of *G. aparine,* a study done to identify the mechanism of action of this plant, showed that *G. aparine* herb contains bioactive fractions made of polysaccharide complex, pectin complex, and polyphenolic complex that stimulate the activity of immunocompetent blood cells and increase the percentage of proliferation of lymphocytes in the lymphocyte blast transformation Google Scholar especially the 96% ethanolic extract of this plant. In addition, these fractions act as direct scavengers of nitrogen oxide (NO), H_2O_2 (hydrogen peroxide), and (2,2-diphenyl-1-picrylhydrazyl) DPPH radical giving the cleavers their antioxidant potential [27].

Other researchers revealed that iridoids exhibit a variety of functionalities including immunomodulatory, antidiabetic, hepatoprotective, choleretic, neuroprotective, and antibacterial activities [34]. Concerning asperuloside, an iridoid isolated from some *Galium* species, it was shown to be responsible for the plant sedative effects, and based on that data, *G. verum* was proven beneficial in nervousness and phobias [14]. Moreover, other researchers investigated the importance of ether terpenes which are responsible for the anti-tumor activity of iridoids because they can inhibit the activity of DNA polymerase [35]. Interestingly, the versatile health benefits of iridoids were shown to be related to the presence of specific oxidative substituents in the cyclopentane ring of the iridoids [36].

More studies were done also to evaluate the anthraquinone mechanism as bacteriostatic and showed that these compounds inhibit bacterial biofilm formation, protein, and nucleic acid synthesis and cause the destruction of bacterial cell walls [37]. These phytochemicals have an anticancer activity which is related to the substitutions of the anthraquinone ring mainly at C-1, C-2, C-3, and C-6 positions, and their anti-pathogenic effect is related to the substitutions at C-1 and C-2 positions while the substitution of the hydroxyl group on the anthraquinone ring is related to most of the activities including the antioxidant and anti-tumor. Moreover, as the polarity of the anthraquinones is stronger, the better is the antibacterial potential of the *Galium* species rich in anthraquinones such as *Galium sinaicum*, *G. verum,* and *G. mollugo* against drug-resistant bacteria including Gram-positive and Gram-negative bacteria. Anthraquinones also exhibit their antibacterial activity by the inhibition of nucleic acids and protein synthesis, and of the respiratory metabolism of bacteria [38]. Furthermore, triterpene saponins have a wide antifungal and antimicrobial potential associated with a specific moiety mainly the aglycone part, and the hydroxyl group esterification affects their effect [39]. These phytoconstituents have a wide biological activity including anti-tumor, anti-inflammatory, and antiviral, and these effects are related to a specific moiety mainly the type of aglycone and the number of sugar chains. The data revealed the antimicrobial properties of some *Galium* species such as *Galium rivale,* are due to the interaction between the sterols on the bacterial erythrocyte membrane and the saponins [40].

Recent studies demonstrated that the antibacterial activity of *Galium* species mainly *Galium aladaghense, Galium incanum*, and *Galium dieckii* is related also to the essential oils obtained from the whole plant, this essential oil comprised around 61 compounds including sesquiterpene (14.75%), monoterpenoid (14.75%), monoterpene(8.2%), and these metabolites exhibit a potent inhibitory potential against Gram-negative and Gram-positive bacteria including *Staphylococcus aureus (S. aureus), Escherichia coli (E. coli), Pseudomonas syringae (P. syringae), Salmonella Typhimurium (S. typhimurium*), and *Streptococcus mutans (S. mutans*) [44]. Accordingly, the mechanism of antibacterial effect is related to a specific moiety, especially the Phenolic-OH present in the essential oil or in the phenolic compounds in addition to the hydrophobicity of the aromatic ring that increases the destruction of the yeast plasma membrane driving to a higher antifungal activity [45]. In conclusion, the structure-activity relationship of the phytochemicals obtained from plants of this genus was demonstrated to illustrate the rationale behind their medicinal uses. The

diversity of the constituents and their evolving biological activities could pave the way for advancing the field of drug discovery and enriching the pharmaceutical industry worldwide. The data illustrated in this study were compiled in a systematic manner to show all the phytochemicals and biological effects collectively. Accordingly, the significance of the analyses done on the collective data facilitates the rapid development of phytochemical research in the direction of drug discovery based on *Galium* plants. Special emphasis on anti-cancer activities to offer a pool of sustainable data that could serve the continuous needs of novel drugs in this regard.

CONCLUSION

Based on the previously mentioned information, the present study demonstrates that *Galium* plants are rich in secondary metabolites of versatile chemical structures including phenolic compounds, triterpene saponins, phytosterols, anthraquinones, and essential oils responsible for the pharmacological potential of these species. The most prominent studies highlighted their antimicrobial, anti-cancer, antioxidant, and anti-inflammatory properties which are all related to a specific moiety in the phytoconstituents such as the phenolic-OH that is common in almost all *Galium* species and which affects the antioxidant and antibacterial potential of these plants based on the number and position of these groups, in addition to the position of substitution of the hydroxyl group on the anthraquinone ring that affects the *Galium* activities mainly those rich in anthraquinones as *G. sinaicum*, *G.verum* and *G. mollugo*. As well as the number of thymol groups, the type of aglycone and the number of sugar chains in other *Galium* species rich in essential oils and saponins such as *G. odoratum, G. aladaghense, G. incanum, G. dieckii,* and *G. rivale.* Accordingly, based on the diversity of therapeutic uses of *Galium*, and since there is a lack of comprehensive studies that summarized the pharmacological potential of *Galium* species, our work is considered as a cornerstone that opens the way for novel approaches in drug discovery based on *Galium* plants growing worldwide. Accordingly, it is highly recommended that future studies investigate the anti-cancer effect of *Galium* plants to make them possible candidates for anti-cancer medicinal products, especially since few researches have been performed on the effect of this plant on cancer cell lines.

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AUTHOR CONTRIBUTIONS

MAK, MAH, AL, MA, made a significant contribution to the work reported, whether that is in the conception, execution, acquisition, analysis, or interpretation of data, or all the areas; took part in drafting, revising, or critically reviewing the article; and gave final approval of the version to be published. All have read and agreed to the published version of the manuscript**.**

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The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

The data that support the findings of this study are available in standard research databases such as PubMed, Science Direct, or Google Scholar, and/or on public domains that can be searched with either key words or DOI numbers.

USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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