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Ethnopharmacology, pharmacological activities, and chemistry of the *Hypericum* genus

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ABSTRACT

There are over 500 species in the *Hypericum* genus worldwide. Crude extracts from Hypericum species have been reported in folkloric medicine as analgesics, anthelmintics, astringents, antidepressants, diuretics, and anti-inflammatories. The current review aims to provide an in-depth analysis of local uses, pharmacological activities, and phytochemical composition of different extracts generated from *Hypericum* species. The review data was collected via literature search from Google, Google Scholar, Medline, Pubmed, Mendeley, Science Direct, Chemical Abstracts, Web of Science, and Scopus. The most studied of the entire Hypericum genus is *H. perforatum*, approved to manage mild depression. Other species that have been reported to have ethnomedicinal value are *H. erectum, H. monogynum, H. attenuatum, H. japonicum, H. beanii, H. monantheum, H. wightianum, H. scabrum, H. monogynum, H. monogynum, H. geminiflorum, H. ascyron, H. seniawinii, H. elodeoides, H. petiolulatum, H. wightianum, H. hengshanense, H. japonicum*, and *H. revolutum*. Over 900 phytochemicals have been isolated from the Hypericum genus plant species, mostly phenolics, and terpenoids. Studies have been carried out to validate the ethnopharmacological use of extracts from *Hypericum* species against depression, cancer, inflammation, and microbial infections. There are limited safety studies involving medicinal plants from the *Hypericum* genus; however,further investigations on toxic effects, phytochemical composition, and biological activities are necessary to validate the medicinal uses of plant species of the *Hypericum* genus empirically. The present article reviews ethnopharmacology, phytochemistry, and toxicology of *the Hypericum* genus, which several communities have used to treat various conditions.

Keywords: *Hypericum* genus, Toxicology, Pharmacology, Chemistry, Traditional use, Ethnopharmacology

INTRODUCTION

The genus *Hypericum* comprises more than 500 species widely distributed globally, except in the Arctic, low-lying tropics, and desert regions [1, 2]. The diverse range of plant species of the genus *Hypericum* are ethnomedically used in Africa, Europe, Asia, and America as analgesics, febrifuges, antidepressants, diuretics, astringents, and anti-inflammatories[3–5]. Notably, *H. perforatum*, usually known as St. John's wort, is the most prominent species in the genus *Hypericum*, which has been studied across time [5–7].Upper leaf and inflorescence extracts of *H. perforatum* are well-established ethnomedicines used to treat mild- to moderate degrees of mental depression across the world [3, 7]. *Hypericum* species have been extensively utilized in traditional medicine to treat diarrhoea, wounds, stings, and bites, and burns, among others [8].

Various phytochemical and pharmacological investigations have revealed antimicrobial, antitumor, antidepressant, and analgesic bioactivities of the *Hypericum* species [9, 10]. These pharmacological effects are attributable to the xanthones, phloroglucinols, essential oils, naphthodianthrones, and anti-inflammatory phytocompounds synthesized by plants of the genus *Hypericum* [11–14]. However, a focused and harmonized recapitulation of the ethnopharmacology, chemistry, and toxicity of medicinal plants of the genus *Hypericum* is lacking, hence the present review. Accordingly, this review explores the ethnomedical uses, chemistry, pharmacology, and toxicity of the genus *Hypericum* to offer updated information, which may guide future empirical studies.

METHODOLOGY

We used relevant key terms, including *Hypericum* species, ethnopharmacology of *Hypericum* genus, Phytochemistry of *Hypericum*, Medicinal uses of *Hypericum*, Bioactivity of *Hypericum*, the safety of *Hypericum*, Antimicrobial activity of *Hypericum*, the anticancer activity of *Hypericum*, Toxicity of *Hypericum*, among others, to garner appropriate literature for this review. These key terms were searched in Scopus, Science Direct, Google Scholar, Medline, PubMed, Mendeley, Chemical abstracts,

and Web of Science, from which we retrieved research articles, review articles, Theses, Books, and Book chapters for review.

ETHNOPHARMACOLOGY OF *HYPERICUM* GENUS

Hypericum species have been instrumental in treating various diseases and conditions in traditional medicine globally. For instance, *H. erectum, H. monogynum, H. attenuatum, H. japonicum*, among others, are used in the Chinese Traditional Medicine as remedies for the irregular menstrual cycle in women, hepatitis, wounds and bruises, jaundice, metrorrhagia, dysentery, acute mastitis, snake bites, burns, sore furuncles, epistaxis, hemorrhages, and hemoptysis [10, 12, 15].

Furthermore, the root and leaf extracts of *H. beanii, H. monantheum, H. wightianum*, and *H. scabrum* are traditionally used for rheumatism, detoxification, promotion of blood circulation, relief of menstrual pain, removal of blood stasis, and to clear heat [16, 17]. Another plant, *H. monogynum*, is a vital ingredient of *lian Qiao* in the Chinese traditional medicine practice to treat stings and bites and trauma caused by blunt objects [12]. The root sap and decoction of *H. monogynum* is used to treat rheumatoid arthritis and hepatitis. Additionally, fresh flower and leaf decoctions are taken simultaneously with topical applications to cure sore furuncles, whereas fruits are consumed to suppress coughs [11, 12].

H. geminiflorum is traditionally used to treat gastrointestinal disorders, bacterial diseases, and infectious hepatitis in affected patients [11]. A decoction of *H. ascyron* twigs is applied as a muscle relaxant and promoter of blood circulation, whereas an external fresh root and leaf poultice is used to treat venomous snake bites [18, 19]. On the other hand, *H. sampsonii* is used to manage irregular catamenia, wounds, and bedsores [20].

In many Traditional medicine practices globally, *H. seniawinii, H. elodeoides, H. petiolulatum, H. wightianum*, and *H. hengshanense* are, especially in Asia and Africa, used as astringents, antidiarrheal, and detoxifying agents. Additionally, *H. elodeoides* and *H. seniawinii* are ethnomedical remedies for indigestion, burns, hepatitis, stomatitis, mastitis, and pneumonia in both children and adults, in China, Turkey, and across the world [2, 12, 21].

The most familiar medicinal plant under the genus *Hypericum*: *Hypericum perforatum* (St. John's wort), has a long history of use as an antidepressant in the European traditional medicine practices [3, 21]. However, ethnomedical literature on its usage in treating mental-associated disorders in Africa and Asia are scanty. Nevertheless, *H. perforatum, H. erectum*, and *H. attenuatum* have been used over time to treat diarrhea, traumatic hemorrhage, endemic cardiomyopathy, metrorrhagia, acute mastitis, hemoptysis, rheumatism, wounds, burns, venomous stings and bites, and antidiuresis across Asia and Africa [5, 11, 22, 23].

Other studies have indicated that *H. japonicum* is used to treat bacterial infections and infectious hepatitis [16]. Besides, *H. hirsutum* is used as a cure for hematochezia, irregular menstrual periods, and hematemesis in Asia [12].

In Kenya, *H. revolutum* subsp. *keniense* is the most common medicinal plant of the *Hypericum* genus in the Hypericaceae family. This plant's leaf, stem, twig decoctions are used to treat joint pains, diarrhea, rheumatism, nervous disorders, skin burns, wounds, and lesions [24, 25].

CHEMISTRY OF THE GENUS *HYPERICUM*

Qualitative phytochemical screening of *Hypericum* genus

Qualitative evaluation of various phytochemical groups in plants of the genus *Hypericum* has been widely conducted. The major phytocomponents of medicinal plants include polyphenolics (flavonoids, quinones, tannins, and coumarins), terpenoids and triterpenes, steroids, saponins, alkaloids, glycosides, essential oils, polypeptides, and minerals [11, 26–28]. The presence of these active principles in plants indicates its pharmacologic significance.

Qualitative phytochemical screening of the acetone and methanol extracts of *H. alpestre* from Armenia revealed phenolic compounds, tannins, flabotannins, and steroids flavonoids and coumarins. However, terpenoids, glycosides, and alkaloids were absent [29]. Notably, the presence of phenols, flavonoids, phloroglucinols, tannins, xanthones, steroids, and coumarins has been preliminarily reported in various plants of the *Hypericum* genus; however, only a handful of bioactive compounds have been isolated and characterized [30, 31, 40, 32–39]. Therefore, further bioassay-guided isolation and characterization of promising phytocompounds are warranted.

Quantitative phytochemical analysis of *Hypericum* genus

Quantitative phytochemical analysis of various *Hypericum* species has revealed an abundance of distinct phytochemical groups. The major phytoconstituents present in *Hypericum* species include naphthodianthrones, such as psedohypericin and hypericin; phloroglucinol derivatives like hyperforin and adhyperforin, and flavonoids such as rutin or quercitrin and hyperoside [41].

Smelcerovic *et al*. [41] analysed the phytochemical composition of six *Hypericum* species from Serbia. Their study indicated that the extract of *H. barbatum* had the highest concentration of hypericin and pseudohypericin. On the other hand, the highest concentrations of quercitrin and hyperforin were observed in the extract of *H. tetrapterum*, whereas the highest hyperoside content was in the extract of *H. maculatum*. Notably, hypericin was present in all the six studied species. However, significant differences in quantitative phytochemical composition *Hypericum* species collected from the same location were observed, denoting the potential role of genetic factors in the production of secondary metabolites in plants [41].

Sagratini *et al*. [42] reported phytochemical composition of eight *Hypericum* species collected from central Italy. The results showed that *H.tetrapterum* and *H. hyssopifolium* had the highest concentration of chlorogenic acid (4.56mg/g-5.00mg/g). The extract of *H. hyssopifolium* showed the highest concentration of rutin (12.42mg/g) compared with the other species. Besides, *H. veronese* extract container higher concentrations of hyperoside, isoquercitrin, quercitrin, quercetin, and hyperforin, than the other extracts. However, hypericin, was not detected in *H. tetrapterum* extract. Other studied *Hypericum* species include *H.majus, H. hirsutum*, and *H, montanum* and all contained the detected compounds, though at lower concentrations. All these compounds have been shown to harbor diverse pharmacologic activities. Quantitative phytochemistry of other *Hypericum* species has been done elsewhere and is still ongoing. Future studies should focus on optimization, further characterization, and empirical validation of phytocompounds in the *Hypericum* genus.

Isolated phytocompounds from the genus *Hypericum*

Over 900 phytochemicals, including flavonoids, phloroglucinols, naphthodianthrones, phenolics, terpenoids, and xanthones, have been isolated from various *hypericum* species [43]. Notably, most of the compounds so far isolated from *Hypericum* species are phloroglucinol derivatives. Figure 1 shows examples of major phytocompounds of *Hypericum* species.

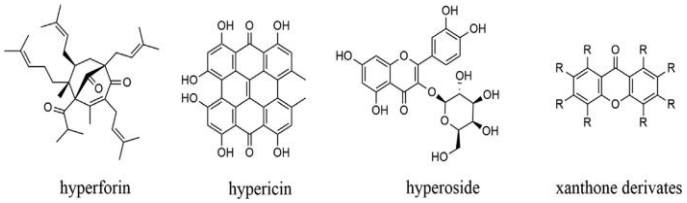

Figure 1: Some of the compounds isolated from the *Hypericum* genus

Polycyclic polyprenylated acylphloroglucinols comprise a class of hybrid natural products with diverse structural and biological properties [43, 44]. Previous studies have revealed that *Hypericum* species are the major sources of more than 700 polycyclic polyprenylated acylphloroglucinol derives [44]. Zhang *et al*. [12] have recently compiled 355 phloroglucinol derivatives that have been isolated from various plants of the genus *Hypericum* over five years. Their study also indicates that apart from phloroglucinol derives, associated antioxidant phytochemicals [45], such as phenolics, flavonoids, xanthones, coumarins, terpenoids, essential oils, and naphthodianthrones have been isolated.

PHARMACOLOGY AND TOXICOLOGY OF *HYPERICUM* GENUS

Despite the extensive utilization of the *Hypericum* genus in traditional medicine to treat various diseases and conditions, there are insufficient empirical pharmacologic studies to validate the claimed healing properties. Therefore, this review sought to consolidate and summarize the available literature on pharmacological investigations of *Hypericum* species. Various bioactivities, including cytotoxicity against cancer cell lines, anticancer, antibacterial, antioxidant, anti-inflammatory, antiviral, antidepressant, anti-α glucosidase, have been documented [46–49, 50–52].

Antidepressant activity

Previous studies have demonstrated the antidepressant efficacy of the *Hypericum* species, especially *H. perforatum* owing to its ethnomedical usage in Europe to treat mild to moderate cases of depression [22, 53]. The proposed mechanisms of antidepressant bioactivities of *Hypericum* species include the inhibition of synaptosomal reuptake of 5-HT, N.A., DA, γ-aminobutyric acid, and L-glutamate in the central nervous system, inhibition of monoamine oxidases, alteration of monoamine transporters and serotonin receptors [53, 54].

The antidepressant properties of *Hypericum* species are attributable to various phytoactive constituents such as hyperoside, hyperforin, and hypericin [55]. Based on these studies, further investigations of other plants of the genus, including *H. longistylum* [12], *H. enshiense* [56], *H. wightianum* [52, 57], and *H. scabrum* [58, 59], for their antidepressant efficacy have been conducted and indicated corroborating results.

Antiproliferative and cytotoxicity

In vitro screening of over 50 phloroglucinol derivatives has revealed their cytotoxic effects against various cancer cell lines. For instance, Li *et al*. [19, 60, 61] reported the *in vitro* antiproliferative activity of an ethanol-water (6:4v/v) extract of *H. ascyron* on the HepG2 human hepatoma MDA-MB-231 breast cancer, HeLa, and HCT-8 human intestinal adenocarcinoma cell lines. In their studies, the extract depicted varied antiproliferative activities with IC_{50} values of 106.9 μg/mL on HepG2, 77.1 μg/mL on MDA-MB-231, 97.7 μg/mL on HCT-8, and 37.2 μg/mL on HeLa cell lines [42].

Furthermore, bioassay-guided fractionation of this extract led to the isolation of kaempferol 3-O-β-(2″-acetyl) galactopyranoside and quercetin, which were cytotoxic to the HeLa cell line (IC_{50}=21.9μM) [19, 43]. However, the authors did not include a positive control in their studies and did not investigate the pharmacologic mechanism of action, requiring further investigations.

Besides, various parts of *H. patulum* have been demonstrated to possess cytotoxic effects against various types of cell lines such as the kidney epithelial Vero cells (IC_{50}=2.2 μg/mL) Human Epithelial type 2 (HEp-2) cell line (IC_{50} =1.7 μg/mL), and rhabdomyosarcoma (R.D.) cells (IC_{50}=1.5 μg/mL) [62]. Another study by Liu *et al*. [63] showed that a phloroglucinol derivative, Hyperpatulol D, isolated from the flowers of *H. patulum*, imparted antimigration effects on U2-OS human osteosarcoma cells in a dose-dependent manner (12.5–50 μM) by downregulating the expression of Vimentin and upregulating the expression of E-cadherin. Since these studies are preliminary, extensive investigations and metabolomic profiling may establish the bioactive molecules which are responsible for pharmacologic and cytotoxic properties of *H. patulum.*

On the other hand, an ethanolic extract of *H. sampsonii* deters the growth of SMMC-7721 liver cancer cells (IC_{50} =49 μg/mL), NIH–H460 lung cancer cells (IC_{50}=38 μg/mL), and MGC-803 stomach cancer cells (IC_{50}=52 μg/mL) via the modulation of the subcellular localization of retinoid X receptor-α [64]. However, a comparison between the potencies of this extract and reference drugs were not made. Therefore, further investigations and bioassay-guided isolation of bioactive compounds are warranted.

Elsewhere, the petroleum ether, dichloromethane, and methanol fractions of *H. scabrum* are cytotoxic and induce apoptosis in the HT-29 colorectal adenocarcinoma cells, MCF7 human breast cancer, HepG-2 hepatocellular carcinoma, and A-549 human lung adenocarcinoma cell lines [65].

Moreover, the petroleum ether and dichloromethane and fractions showed IC_{50} values of 22.6 μg/mL and 25.7 μg/mL and against HT-29 cell using 5-fluorouracil as positive control (IC_{50} = 4.8 μg/mL), and 24.7 and 18.3 μg/mL in HepG-2 cell with 5-fluorouracil as positive control (IC_{50} = 7.6 μg/mL). Additionally, the petroleum ether and methanolic fractions of *H. scabrum* activated caspase-3 and Annexin, thereby inducing apoptosis. Notably, due to the promising anticancer potential of phloroglucinol and phenolic phytocompounds of *Hypericum* species, many studies are at their preliminary stages and ongoing. Perhaps, these studies may lead to the discovery and development of potent anticancer agents from *Hypericum* species [65].

Antimicrobial activity

Several medicinal plants of the genus *Hypericum* have shown antimicrobial activities on various strains. For instance, the alcoholic aqueous extract of *H. ascyron* has antibacterial activity against *M. luteus*, *Staphylococcus aureus*, and *Escherichia coli* mediated by induced membrane apoptosis [19]. The antimicrobial efficacy was attributed to kaempferol 3-O-β-(2-acetyl) galactopyranoside and quercetin, obtained via bioassay-guided fraction [66].

Chloroform, acetone, and methanol leaf and stem extracts of *H. hookerianum*, at concentrations of 300 µg/mL, inhibit the growth of *Bacillus megaterium, Pseudomonas cepacia, Staphylococcus aureus, Bacillus subtilis, Bacillus coagulans*, and *Escherichia coli* [67]. Petroleum ether, chloroform, acetone, and methanol leaf and stem extracts of *H. patulum*, at concentrations of 800 µg/mL, inhibits *P. cepacia, B. subtilis, B. megatorium, S. aureus, E. coli, B. coagulans, Candida albicans, Cryptococcus neoformans*, and *Candida tropicalis* [68].

In a recent study by Doğan *et al*. [69], 250 µg/mL of the acetone, ethanol, and methanol extracts of *H. perforatum* significantly down-regulated las and rhl associated genes' expression in *P. aeruginosa*; however, these extracts did not inhibit biofilm formation, suggesting that biofilm formation could be via the integrated quorum sensing or *Pseudomonas* quinolone signaling systems.

An earlier study indicated that the leaves, flowers, stem, and stem bark of *H. revolutum* subsp. *keniense* have saponins, cardiac glycosides, flavonoids, tannins, coumarins, carotenoids, and volatile oils. Aqueous and methanolic extracts have been shown to have antibacterial and antifungal activities [70].

Extracts of *H. scabrum* have demonstrated significant antimicrobial efficacies on several microbes like *B. cereus* and *Salmonella. typhimurium* [47], *E. coli, L. monocytogenes, P. vulgaris, B. megaterium, P. aeruginosa, Klebsiella pneumoniae, B. subtilis, S.* aureus and *C. albicans* [49], *C. perfringens* [71], *E. faecalis, A. niger, S. epidermidis*, and *S. cerevisiae* [72,73], *S. pyogenes, E. cloacae*, and *K. oxytoca* [12] and *B. brevis* [74]. Besides, phytocompounds isolated from roots of *H. ascyron* [75], the whole plant of *H. japonicum* [76], and leaves of *H. patulum* [77] are the most promising potential source of antimicrobials based on their low MIC values (0.8–16 µM). The major antimicrobial activity associated with phytocompounds of *Hypericum* species includes xanthones [78], phloroglucinol derivatives [77], flavonoids [79], and other phenolic derivatives [80].

Antiviral activity

Various compounds isolated from the aerial parts of *H. japonicum*, among other *Hypericum* species, such as hyperjaponol D, (+)-Hyperjaponol B, filicinic acid-based meroterpenoids and (−)-hyperjaponol B moderately inhibit DNA replication in lytic Epstein-Barr virus B95-8 cells (EC_{50} values= of 0.5-6.6 µM), with ganciclovir as a positive control (EC_{50} = 2.9 µM. Other isolated analogs like (+)-Japonicols B, E, and H, and japopyrone B, isolated from the aerial parts of *H. japonicum* [18, 81, 82], significantly inhibit Kaposi's sarcoma-associated herpesvirus in Vero cells (EC_{50} values=4.9-29.5 µM).

Notably, most previous studies did not include standard drugs, which cripple confidence in the findings. Nevertheless, there exists pharmacologic evidence that supports the antiviral potential of *H. japonicum* among other *Hypericum* species. Future studies should focus on action mechanisms and optimization of the most promising antimicrobial compounds [18, 81, 82].

Anti-inflammatory activity

The anti-inflammatory activities of the *Hypericum* species have been demystified scientifically, leading to the isolation of over 36 compounds with promising efficacy. Of the isolated compounds, polycyclic polyprenylated acylphloroglucinols from *H. monogynum* (Xu *et al*., 2015, *H. ascyron, H. beanii* [83–85], *H. sampsonii* [86], and *H. patulum* [63], and phenolic compounds isolated from *H. sampsonii* [20, 63], *H. erectum* [51], *H. elatoides* [87] and *H. monogynum* [88, 89] inhibit NO production in LPS simulated RAW 264.7 or BV2 cells *in vitro*, (IC_{50} =1.4 to 36.8 µM), depicting their anti-inflammatory potential. However, there are scanty *in vivo* and mechanistic studies to validate these bioactivities.

Neuroprotective activity

Oliveira *et al*. [22] suggest quercetin, quercitrin, hyperoside, hyperforin, rutin, biapigenin, hypericin, and kaempferol in *H. perforatum* have neuroprotective potency. Moreover, 45 compounds including flavonoids, benzophenones, phloroglucinols, xanthones and biphenyl ether glycosides isolated from *H. ascyron* [46], *H. wightianum* [90, 91], *H. elatoides* [91], *H. acmosepalum* [92], and *H. monogynum* [46] have demonstrated neuroprotective efficacy chemical-induced neurodegenerative rat pheochromocytoma PC12 cells and human neuroblastoma SK-N-SH and SH-SY5Y cell lines. However, further *in vivo* studies should be conducted to appraise the neuroprotective potential of the isolated phytocompounds.

Anti-plasmodial activity

Considering the public health threat posed by malaria in Africa, Zofou *et al*. [93] performed a bioassay-guided fractionation of the stem bark of *H. lanceolatum* as a potential source of new antimalarial agents. This study's findings demonstrated a good *in vitro* antiplasmodial activity of the ethyl acetate fraction (IC_{50} < 10µg/mL) on W2mef strain of *P. falciparum*. Further, the n-butanol, ethyl acetate, methanolic and aqueous sub-extracts were relatively noncytotoxic on the monkey kidney epithelial cells (LLC-MK2) and exhibited CC50 values of >30µg/mL as per the previously described criteria [35, 36, 94].

Furthermore, 3hydroxy-lup-20(29)-en-28-oic acid (betulinic acid) and 5-hydroxy-3-methoxyxanthone demonstrated good anti-plasmodial activity against W2mef strain depicting their antimalarial potential [93]. However, another promising compound code-named HLT0 was not identified in this study. Additionally, this study did not attempt to investigate the mechanism of action of the isolated active compounds and their interaction effects, which call for further characterizations.

Besides, Moon [95] investigated the anti-plasmodial and cytotoxic effects of phloroglucinol derivatives from the chloroform extracts of *H. erectum* on chloroquine-sensitive *P. falciparum* strain and SK-OV-3 cancer cell line. The findings showed that out of the five phloroglucinol derivatives, otogirin (1), otogirone (2), erectquione A (3), erectquione B (4), and erectquione C (5), only otogirone (2) anderectiquinone B (4) exhibited notable anti-plasmodial effects with IC_{50} values of 5.6 and 7.2 µM. However, these compounds did not exert significant cytotoxic effects on SK-OV-3 cells ((IC_{50} > 150 µM) [95]. Notably, this study did not study the interaction effects and their mechanism of action.

Nevertheless, since the results presented are only preliminary, there is a need for extensive studies using other methods and strains and *in vivo* investigations to empirically validate the pharmacologic potential of *H. erectum* and *H. lanceolatum* as sources of antimalarials in the future.

Antioxidant activity

The antioxidant potency of medicinal plants is associated with a broad spectrum of pharmacologic activities, including cognitive enhancement, antimicrobial, anti-inflammatory, antidiabetic, anticancer, immunomodulatory, antiaging, anti-neurodegeneration, among others [45, 96–103].Various Hypericum genus plants have antioxidant properties attributable to the enormous amounts of antioxidant-associated secondary metabolites [22]. For instance, ethanolic and hydroethanolic extracts of *H. perforatum* inhibits malondialdehyde (MDA) formation in the brain of scopolamine-induced amnesic rats, indicating its oxidative-stress ameliorating efficacy [104]. Also, in equivalent doses to the *H. perforatum* extracts used to manage depression, modulates glutathione peroxidase and glutathione activity levels, thereby quenching oxidative stress. Elsewhere, extracts of *H. perforatum* have been demonstrated to scavenge 1,1-diphenyl-2-picryl-hydrazyl (DPPH) radicals *in vitro*, positing EC_{50} values of between 49.3±1.05µg/ml to 109µg/ml. Besides, these extracts deter Xanthine oxidase activity (IC_{50}=68.3µg/ml; 16 % inhibition of X.O.), depicting antioxidant potency.

The aqueous and ethanolic extracts of *H. perforatum* inhibits lipid peroxidation caused by 2,2'-azo-bis(2-methylpropioanamidine) dihydrochloride (AAPH) (IC50=50.4 ± 2.57 µg/dwb/mL), thereby limiting the production of peroxyl radicals. These extracts have also been shown to scavenge NO radicals by reducing nitrite release [104].

In vivo studies have demonstrated the efficacy of *H. perforatum* in deterring MDA formation and potentiating endogenous antioxidant enzyme (Catalase, Superoxide mutase, and glutathione peroxidase) activities in brains of rotenone-induced oxidative stress [104]. Perhaps these findings partly explain the efficacy of this plant in alleviating depression and other neurodegenerative diseases.

On the other hand, the leaf and flower extracts of *H. mysorense* demonstrated remarkable antioxidant activity against the DPPH, NO, O_2, and OH radicals [33]. These potencies were attributable to their high total phenolic and flavonoid contents. Furthermore, these extracts significantly downregulated 2-thiobarbituric acid reactive substance (TBARS) while upregulating SOD and CAT activity levels. Quantitative phytochemistry by HPLC analysis revealed the presence of rutin and hyperoside, which possess antioxidant properties [33].

Elsewhere, the methanolic and aqueous extracts of *H. lydium* scavenge the DPPH radicals giving IC_{50} values of 76.24±1.84 µg/mL and 168.64±0.91 µg/mL, respectively [104]. The ethanolic extract of aerial parts of *H. lydium* is an efficient scavenger of the DPPH radical (IC_{50}= 0.165±0.23 mg/mL, denoting its *in vitro* antioxidant efficacy [105]. Due to its antioxidant potency and safety, *H. lydium* may be instrumental in preventing mutagenesis and cancer. Previous studies have shown that the methanolic extracts of *H. lydium* are better scavengers of the DPPH and ABTS radicals *in vitro* than the aqueous extracts, as evidenced by low IC_{50} values due to the high concentration of polyphenolic phytocompounds [104, 34].

Indeed, the total phenolic content in the methanolic extract of *H. lydium* is 136.45±4.51 GAE µg/g while the aqueous extracts contain 68.93±2.82 GAE µg/g. Similarly, the total flavonoid content in the aqueous extract of *H. lydium* was 4.97±4.56 C.E. µg/g compared with 156.44±5.51 C.E. µg/g in the methanolic extract [104]. The antioxidant efficacies are attributable to these phytocompounds.

Besides, a study by Huang *et al.* [106] showed that the main flavonoid of *H. japonicum* (Quercetin 7-rhamnoside) demonstrated significant antioxidant efficacy upon DPPH, ABTS, and FRAP *in vitro* assays. Upon the induction of oxidative stress in the human liver L-02 cells using H_2O_2, Quercetin 7-rhamnoside exerted cytoprotective and antioxidant effects. Furthermore, this compound suppressed MDA production and upregulated antioxidant enzyme activities such as the catalase, indicating its potential in ameliorating oxidative stress-induced hepatic injury [106]. However, specific mechanisms, optimal doses, and clinical studies should be performed to establish the pharmacologic significance and applicability in clinical settings.

Toxicity

The widespread usage of *Hypericum* species in traditional medicine has raised safety concerns. Despite most of them, including the commonest plant, *H. perforatum*, recording appreciable safety profiles, its combination with conventional medicines and other herbal formulations in various health states have been shown to evoke adverse effects [107–109]. For instance, *H. perforatum* has been demonstrated to cause teratogenic effects in newborns. Additionally, the phytoconstituents such as hypericins of *Hypericum* species are responsible for their toxicities, including phototoxicity and psychosis [37, 38, 110–115]. However, toxicological studies on this genus are far and between, thereby calling for further and extensive safety and toxicological profiling.

CONCLUSIONS AND FUTURE PERSPECTIVES

Various *Hypericum* species are extensively utilized in traditional medicine to treat a wide range of ailments asserting their critical role in primary healthcare. The presence and pharmacologic potency of several phytochemical compounds produced by the *Hypericum* species offer a potential source of future drugs against microbial, inflammatory, mental, cancer, among other associated diseases, currently affecting humankind globally. Notably, most pharmacologic studies are in their preliminary stages; hence further investigations and characterizations, including *in vivo* and mechanistic validations, are warranted. Furthermore, to a large extent, toxicological and safety evaluations of the genus *Hypericum* are lacking; therefore, toxicological investigations and safety appraisal of these medicinal plants should be done. The current review presented herein is not exhaustive and is based on the available literature; hence more emerging studies may foster and shape future research on *Hypericum* species.

Author contributions

Omambia Vincent garnered the literature and drafted the manuscript. Fredrick Musila, Dorine Nyak, Ali Hashim Mohammed, and Moriasi Gervason enhached the quality of the manuscript through rigorous review, criticism, andliterature enrichment. Joseph Nguta and Simon Mitema supervised the study.

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Conflict of Interest

The authors declare no conflict of interest regarding this review study.

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