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Exploring the bioactive constituents and medicinal properties of *Hypericum androsaemum* L: A detailed review

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Abstract
Hypericum androsaemum L., native to the Mediterranean region, is renowned for its broad spectrum of medicinal properties, including diuretic, hepatoprotective, antihypertensive, antihemorrhoidal, antidepressant, and skin-protective effects. This review consolidates the pharmacognostic insights into this species, emphasizing its rich phenolic profile, including chlorogenic acids, flavonoids, triterpenoids, polycyclic polyprenylated acylphloroglucinols (PPAPs), and xanthones. The plant's extracts have demonstrated strong antioxidant capabilities, with its fruits notably exhibiting cytotoxic effects against certain cancer cell lines. Additionally, *H. androsaemum* shows promise in immunomodulation, DNA protection, anti-glycation, antidepressant, and anti-inflammatory activities. It also promotes fibroblast proliferation and migration, inhibits collagenase and tyrosinase, and provides UV protection without phototoxic effects, making it a valuable candidate for skincare formulations. Furthermore, *H. androsaemum* extracts display biocidal activity against a range of bacteria, fungi, nematodes, mollusks, and insects, while maintaining low toxicity toward normal cells at minimal concentrations. However, the high hyperforin content raises concerns about the safety of oral consumption, warranting cautious consideration.

Keywords: Phytochemical, biological activities, oil, cytotoxicity

Introduction
Hypericum androsaemum L., also known as sweet amber, tutsan, or "hipericão-do-Gerês," is a small deciduous shrub native to Western and Southern Europe, extending to Northern Africa and Western Asia. It is particularly abundant in northern Portugal, where it thrives in acidic, loamy soils under both full sun and partial shade [1-3]. Renowned for its upright growth, leaf variegation, and striking yellow flowers that bloom from late spring to summer, *H. androsaemum* is extensively cultivated as an ornamental plant. The plant also produces fleshy, berry-like fruits that transition from red to black as they mature, adding to its visual appeal and aiding in seed dispersal by attracting birds [4-6].

The name "tutsan" is derived from the French term "toutsaine," meaning "all-heal," reflecting the plant's historical use in traditional medicine. The ancient Greek physician Dioscorides recommended *H. androsaemum* for treating sciatica and burns, highlighting its therapeutic significance. In Portuguese folk medicine, the plant is known as "erva-mijadeira" or "diuretic herb," and its infusions have been traditionally used to treat kidney and bladder ailments, as well as for hepatoprotective and antihypertensive effects [7-9]. Although *H. androsaemum* does not contain hypericin, the compound primarily responsible for the antidepressant effects of Hypericum perforatum, it has been used as an antidepressant and anxiolytic in Portuguese and Spanish folk medicine. This usage is supported by the neuroprotective and antidepressant activities of its phenolic compounds.

In addition to its use in Iberian traditions, *H. androsaemum* has also been employed in England and Iran to treat hemorrhoids and to prepare ointments for cuts and wounds. Despite its medicinal benefits, the plant's invasive potential in regions like Australia and New Zealand requires careful management to prevent ecological imbalance [10-12]. These attributes make *Hypericum androsaemum* a valuable ornamental species and an important part of traditional medicine across various cultures.

Materials

A comprehensive literature review was conducted in August 2023 to gather information on *Hypericum androsaemum*. The initial search was performed on PubMed using the keyword "*Hypericum androsaemum*" across the full text without applying any date restrictions. This search yielded 37 relevant publications. To expand the scope of the review, a supplementary search was conducted on Google Scholar, which provided an extensive array of results. The first 100 entries were carefully examined, and after excluding duplicates from the PubMed search and articles not directly related to pharmacological activities, an additional 8 relevant studies were identified and added to the reference library.

The data compiled in this review provides a comprehensive summary of the phytochemical compounds, ethnomedicinal uses, and pharmacological activities associated with *Hypericum androsaemum*. Notably, this species has been traditionally used in various cultures for its potential therapeutic benefits, including its use as an anti-inflammatory, antibacterial, and wound-healing agent.

Furthermore, during the manuscript preparation phase, an additional 10 articles focusing specifically on the pharmacological properties of individual chemical compounds isolated from *Hypericum androsaemum* were incorporated into the analysis. These studies highlighted the bioactive components, such as hypericin, pseudohypericin, and various flavonoids, which contribute to the plant's pharmacological profile. The therapeutic potential of these compounds has been extensively studied, with particular emphasis on their antidepressant, anti-inflammatory, and antimicrobial effects.

In summary, this review consolidates the current knowledge on *Hypericum androsaemum*, emphasizing its rich phytochemical diversity and the promising pharmacological activities that support its traditional medicinal uses. The integration of recent studies on individual compounds further enriches the understanding of this species' therapeutic potential, providing a solid foundation for future research and development of *Hypericum androsaemum*-based pharmacotherapies.

Phytochemical Active Compounds

Hypericum androsaemum is rich in a variety of phytochemicals, including organic acids, phenolic compounds, flavonoids, triterpenoids, vitamins, minerals, and fatty acids [13-16]. Numerous studies have utilized chromatographic techniques to analyze the chemical composition of different plant parts, revealing a complex profile of secondary metabolites [1, 5, 9, 17, 24].

In recent research, the most abundant compounds identified in the leaves include caffeic acid, with a concentration of 3313±80 µg/g in water extracts. In methanolic extracts of the leaves, significant amounts of (-)-epicatechin (6538±235 µg/g), (-)-epigallocatechin gallate (3035±82 µg/g), myricitrin (3657±113 µg/g), and hyperoside (3713±111 µg/g) were detected. Studies focusing on the aerial parts have consistently highlighted quinic acid, caffeoylquinic acid, quercetin derivatives, catechin, and kaempferol as the major constituents [5, 9, 11, 17, 25].

The red fruits of *H. androsaemum* are particularly noteworthy for their high shikimic acid content, which can reach up to 12.799 mg/g dry weight (DW). Chlorogenic acid and neochlorogenic acid are also prevalent, with concentrations as high as 15 mg/g DW and 6.6 mg/g DW, respectively, in red fruits, though these compounds are less abundant or undetected in black fruits. A study dedicated to the analysis of red berries reported that shikimic acid was the most abundant compound, with a concentration of 115,901±8,284 mg/kg [18-20]. Other significant compounds included chlorogenic acid (57,002±94 mg/kg), catechin (5,770±27 mg/kg), hyperoside (2,831±136 mg/kg), epicatechin (1,887±185 mg/kg), rutin (1,411±207 mg/kg), and neochlorogenic acid (944±30 mg/kg). These findings align with results from other studies [21-23].

The variation in phytochemical composition between red berries, black berries, aerial parts, and leaves can be attributed to the plant's phenological stages. For instance, shikimic acid, a precursor to aromatic amino acids and phenolic compounds, is more abundant during the early stages of development. Chlorogenic acid is primarily accumulated in the leaves, with its levels peaking during the vegetative stage and declining as the plant matures.

Interestingly, *H. androsaemum* lacks the black nodules characteristic of other *Hypericum* species, where naphthodianthrones such as hypericin and pseudohypericin are typically produced. As a result, *H. androsaemum* is free of hypericin, which can be advantageous in certain therapeutic contexts, particularly for skin-related applications, as hypericin is known to cause phototoxicity and can induce hepatic enzyme activation [23-25].

Moreover, *H. androsaemum* is rich in a diverse array of phenolic compounds, including phenolic acids, lignans, quinones, xanthones, and polycyclic polyprenylated acylphloroglucinols (PPAPs). When compared to *Hypericum perforatum*, *H. androsaemum* exhibits higher total phenolic content in most samples analyzed. Among 30 *Hypericum* species evaluated in another study, *H. androsaemum* was found to have one of the highest phenolic acid contents, though it had relatively lower flavonoid levels.

This robust phytochemical profile underscores the potential of *H. androsaemum* for various pharmacological applications, particularly in areas where its unique chemical composition offers advantages over other *Hypericum* species [23-25].

Phenolic Acids

Hypericum androsaemum is particularly rich in chlorogenic acids, which are among the most prevalent phenolic acids in the species. These include several esters of caffeic acid and quinic acid, such as 5-O-caffeoylquinic acid (commonly known as chlorogenic acid), 3-O-caffeoylquinic acid (neochlorogenic acid), and 3,5-dicaffeoylquinic acid. These compounds are known for their diverse biological activities, including antidepressant, antioxidant, and anti-inflammatory effects. They have shown considerable promise in the treatment of depression and in enhancing cognitive functions like learning and memory [25-27].

In addition to chlorogenic acids, *H. androsaemum* contains other phenolic acids such as ferulic acid, fumaric acid, gallic acid, and rosmarinic acid. Each of these compounds contributes to the plant's overall therapeutic potential, with documented effects that include anti-inflammatory, antioxidant, and antimicrobial activities.

Flavonoids

H. androsaemum is also a rich source of flavonoids, encompassing several subtypes such as flavanols (e.g., catechin and its derivatives), flavonols (e.g., quercetin, kaempferol), flavones (e.g., 7-O-glucosyl luteolin, biapigenin, and amentoflavone), flavanones (e.g., eriodictyol-O-glucoside, taxifolin), and various proanthocyanidins. Recent

measurements have shown that the total flavonoid content in dichloromethane extracts from the leaves is approximately 86.47 µg/g, while in the fruits, it is around 9.24 µg/g.

A comparative study found that flavonoids are more efficiently extracted using water infusions rather than methanol. The total flavonoid content reached 2463 mg rutin equivalents per kilogram in red fruits, while in black fruits, the highest content was 1140 mg rutin equivalents per kilogram. Methanol extracts have shown that the most abundant flavonoid aglycones are apigenin, quercetin, and rhamnetin. Quercetin, in particular, is noted for its wide range of biological activities, including antioxidant, anti-inflammatory, antibacterial, antiviral, radical-scavenging, gastroprotective, and immune-modulatory properties. Catechin has been extensively studied for its anti-cancer potential, exhibiting anti-oxidative, pro-oxidative, and anti-inflammatory activities [28, 29, 30, 31].

Polycyclic Polyprenylated Acylphloroglucinols (PPAPs)

PPAPs are a unique group of compounds that contain an acylphloroglucinol core—this includes a phloroglucinol moiety (a benzene ring with three hydroxyl groups) attached to one or more acyl groups, along with various polycyclic and polyprenylated structures. In *H. androsaemum*, the total acylphloroglucinol content in ethanol extracts of the flowering tops is approximately 10.69 mg/g DW, which is about four times less than what is found in *H. perforatum* or *H. perfoliatum*. Specifically, hyperforin and adhyperforin levels have been measured at 9.34 mg/g DW and 1.35 mg/g DW, respectively. The content of hyperforin in methanol extracts of aerial parts varies with the plant's phenological stage, ranging between 0.39 and 2.37 mg/g DW. PPAPs like androforin A and hyperandrone A have also been detected in *H. androsaemum* [32, 33, 34, 35].

PPAPs are known for a range of biological activities, including anti-HIV, antidepressant, antibacterial, antimalarial, antioxidant, anti-neurodegenerative, anti-ulcer, wound healing, and anti-inflammatory effects. Hyperforin, one of the main PPAPs, is particularly recognized for its role in the therapeutic potential of the *Hypericum* genus.

Xanthones

Xanthones are another class of compounds present in *H. androsaemum*, though they are generally less abundant in nature compared to other phenolic compounds. The red coloration of the unripe capsules is due to 1, 2, 3, 5-tetrahydroxyxanthone. Other identified xanthones include 1, 3, 6, 7-tetrahydroxy-8-prenylxanthone, 1, 3, 5, 6-tetrahydroxy-2-prenylxanthone, γ-mangostin, 1,7-dihydroxyxanthone, and cudraxanthone K. Previous studies have isolated hydroxy and methoxy-substituted xanthones from the roots, along with oxygenated xanthones and prenylated xanthone aglycones and their glucosides from the plant. [36,37,38] The accumulation of xanthones in cultured cells of *H. androsaemum* has been found to parallel cell growth, with light exposure and culture medium composition significantly influencing their production. Xanthones possess a range of pharmacological properties, including monoamine oxidase inhibition, antioxidant, antifungal, cytotoxic, and hepatoprotective activities. [39,40,41,42]

Triterpenoids

Triterpenoids identified in the methanol extracts of the aerial parts of *H. androsaemum* include acetyloleanolic acid, β-amyrin, putranjivic acid, and friedelin. Some of these compounds have demonstrated cytotoxic activity against various human cancer cell lines. Additionally, hederagenin and quillaic acid have been detected. The red fruits of *H. androsaemum* are particularly rich in essential oils and monoterpene hydrocarbons [43, 44, 45].

Other Secondary Metabolites

Among other secondary metabolites, the lignan 1,4-O-diferuloylsecoisolariciresinol has been identified in the aerial parts of *H. androsaemum*. This compound has shown strong cytotoxic activity against several cancer cell lines, with efficacy comparable to that of cisplatin. Herniarin, or 7-methoxycoumarin, has also been found in significant amounts in the fruits and is known for its cytotoxic and anti-inflammatory properties [46-48].

Vitamins and Minerals

The unripe fruits of *H. androsaemum* are a notable source of ascorbic acid, with concentrations reaching 136 mg/100g DW. This level is three times lower than in *Rosa canina* fruits but about twice as high as in oranges. Fresh fruits also contain around 1.2% vitamin K and less than 1% calcium (Ca), silicon (Si), and copper (Cu) [49, 50].

Fatty Acids

H. androsaemum fruits are rich in fatty acids, particularly linoleic acid (up to 46.9% DW), linolenic acid (up to 23.03% DW), oleic acid (14.96% DW), stearic acid (11.8% DW), and palmitic acid (10% DW). The ratio of polyunsaturated fatty acids (PUFA) n-6 to n-3 is 2.2 in red fruits and 1.8 in black fruits [51-54].

Essential Oil Composition

Essential oil composition in *H. androsaemum* has been extensively studied, with over 100 components identified. Sesquiterpenoids are the most prominent group in the leaves and flowers, comprising between 43% and 98.5% of the oil composition. In dried leaves from Iran, caryophyllene oxide (35.8%), ishwarane (30.5%), and humulene epoxide II were found to be the dominant molecules. In flowers from the same region, α-guaiene (40.2%) and caryophyllene oxide (28%) were most abundant. Plants from Turkey exhibited germacrene B (31.50%), α-zingiberene (22.75%), α-curcumene (15.21%), β-caryophyllene (14.34%), and naphthalene (11.87%) as major volatile components, depending on the phenological stage. In the northern region of Portugal, the predominant compounds were (E)-caryophyllene, β-gurjunene, and γ-elemene.

In the fleshy red and black fruits from wild and cultivated plants in central Italy, monoterpenoids were the most representative group, accounting for 78.8% to 84.0% of the composition, with limonene (42.9–50.9%), β-pinene (18.8–20.0%), and α-pinene (9.3–12.7%) being the most abundant. The oil yield by dry weight was 0.3%±0.03% in red fruits and 0.1%±0.01% in black fruits. Red fruits had a higher oil yield, a greater amount of monoterpene hydrocarbons (84.0% vs. 78.8%), and a lower amount of sesquiterpene hydrocarbons (11.9% vs. 16.7%) compared to black fruits [50-53].

Several factors contribute to the differences in volatile composition, including collection time, chemotypes, drying conditions, distillation methods, and geographical and climatic influences. Notably, the floral budding.

Biological Activity

Antioxidant Activity

Free radicals, including reactive oxygen species (ROS), are critical triggers for a range of diseases such as degenerative disorders, metabolic issues, and cancer [26]. Oxidative stress is a recognized harmful process implicated in various liver conditions, including metabolic issues, alcoholic liver disease, chronic viral hepatitis, autoimmune liver diseases, and non-alcoholic steatohepatitis, which can progress to degenerative liver diseases and hepatocellular carcinoma. This highlights the ongoing importance of identifying effective antioxidant compounds. Phenolic compounds, in particular, have demonstrated significant antioxidant properties.

The ethanol-water extract of *H. androsaemum* aerial parts has shown antioxidant activity comparable to or exceeding that of ascorbic acid, mannitol, rutin, cysteine, and Trolox when tested against several reactive oxygen and nitrogen species [8]. In another study, this extract exhibited lipid peroxidation inhibitory activity, DPPH scavenging, and reducing power similar to Trolox, although its β-carotene bleaching inhibitory activity was significantly lower than Trolox [26]. The methanol extract of the aerial parts demonstrated radical scavenging ability that was approximately three times less than that of propyl gallate in anion and DPPH tests [38].

Water extracts of the leaves showed markedly higher scavenging activity against enzymatic superoxide radical generation (2.9 µg/mL) compared to non-enzymatic systems (25.6 µg/mL). This indicates that part of the radical reduction effect could be attributed to a moderate non-competitive inhibition of the enzyme generating the radical rather than solely scavenging activity [39]. In the CUPRAC assay, the methanol extract of leaves outperformed the control substance alpha-tocopherol (alpha-TOC) [11].

Among six *Hypericum* species studied (*H. acutum, H. androsaemum, H. barbatum, H. hirsutum, H. maculatum*, and *H. richeri*), all exhibited higher DPPH scavenging activity compared to lyophilized green tea water extract, although with weaker anti-lipid peroxidation activity. *H. androsaemum* showed the highest superoxide anion radical neutralization (EC_{50} = 125 µg/mL), comparable to the green tea extract and approximately twice as effective as Trolox. Unlike DPPH• and ABTS•+, the superoxide anion radical is a reactive oxygen species prevalent in biological systems [24].

The observed radical scavenging activity is largely attributed to the plant's phenolic compounds, primarily chlorogenic acids, catechins, and their derivatives, and quercetin and its derivatives. However, various factors such as concentration, compound synergy, and environmental conditions can influence the mechanisms of these compounds' individual and collective actions.

Cytotoxic and Pro-apoptotic Activity

The methanol extract of black fruits exhibited the highest cytotoxic activity, with IC_{50} values below 20 µg/mL against A375 (malignant melanoma), MDA-MB 231 (breast adenocarcinoma), and CT116 (colon carcinoma). CT116 was the most responsive (IC_{50} = 8.4 µg/mL). Red fruits showed similar activity, particularly against CT116 (IC_{50} = 19.4 µg/mL) [1].

For colorectal cancer cells, a 40% apoptosis rate was achieved in CO115 cells using the total methanol extract at 40 µg/mL, accompanied by a significant reduction in BRaf, pErk, and pAKT expression. The individual fractions did not fully account for the apoptotic activity of the total extract, suggesting possible synergistic effects among several constituents [40].

The water extract of aerial parts inhibited cell proliferation and induced apoptosis through various mechanisms in two colon cancer cell lines, HCT15 (KRAS mutation) and CO115 (BRAF mutation). It reduced BRAF and phospho-ERK expressions in CO115 but not in HCT15 and decreased Akt phosphorylation in CO115 while inducing p38 and JNK pathways in both cell lines. It also caused cell cycle arrest at S and G2/M phases and caspase-dependent apoptosis in both cell lines [41].

The ethanol extract showed substantial cytotoxicity against A1235 (glioblastoma) cells, inducing 43.9% cell death after 72 hours, one of the highest among 16 *Hypericum* species tested. Apoptosis was the predominant cell death type attributed to cell cycle disruptions. Despite hypericin's known cytotoxic effects, its absence in this species is noted; however, hyperforin, present in significant amounts, has pro-apoptotic and tumor-inhibitory activity. None of the species tested showed cytotoxic effects against MDA MB231 (breast cancer cells) [42].

Another study found that the methanol extract of ripe fruits induced weak apoptosis in PC-3 (prostate adenocarcinoma) cells, with 64.75% cell death at 50 µg/mL and weak cytotoxicity (IC_{50} = 74 µg/mL). The leaf extracts were even less effective, with IC50 > 50 µg/mL in the dichloromethane fraction and only 10.54% apoptosis at 200 µg/mL of the total methanol extract. Weak effects were also noted against HepG2 (hepatocellular carcinoma) cells, with the methanol extract of ripe fruits showing the best cytotoxicity (IC_{50} = 32 µg/mL) and the methanol extract of leaves showing the best pro-apoptotic activity (28% cell death at 25 µg/mL) [11].

Ethanol-water extracts of aerial parts showed very weak activity against various cancer cell lines (MCF-7, HeLa, NCI-H460) with GI_{50} values greater than 100 µg/mL, which was approximately 1/100th of the activity of ellipticine [26]. Two compounds isolated from the plant extracts were tested against five human cancer cell lines: HL-60, SMMC-7721, A-549, MCF-7, and SW480. 1,4-O-diferuloylsecoisolariciresinol demonstrated high cytotoxicity against these cell lines, comparable to cisplatin, especially in HL-60 and MCF-7. Acetyloleanolic acid also showed IC_{50} values below 20 µg/mL against HL-60, SMMC-7721, and A-549 [20].

Several compounds from *H. androsaemum* have been identified as cytotoxic against various cancer cell lines, including phenolics like chlorogenic and shikimic acids and flavonoids like quercetin, catechin, epicatechin, rutin, and xanthones. The triterpenoid quillaic acid has demonstrated apoptosis induction potential in colon and gastric cancer cells [1, 41].

However, the biological actions of plant extracts cannot be solely attributed to their major compounds. Synergistic or counteracting effects can occur, involving even minor compounds. For instance, antioxidant activity might interfere with cytotoxic effects by scavenging ROS or competing for light energy. The actual effects depend on cell characteristics, environmental conditions, and other factors. Flavonoids, for example, can exhibit pro-oxidant activity under certain conditions, resulting in cytotoxicity [14, 43]. High concentrations of substances may also lead to toxicity [1]. Isolated compounds do not always yield consistent results; for example, chlorogenic acid alone did not show significant cytotoxic effects against colon cancer cells in one study [41], while another study demonstrated strong inhibition of cell viability through ROS production, S-phase arrest and extracellular signal-related kinase inactivation [44]. Further

investigation is needed to understand the potential of *H. androsaemum* and its compounds in cancer treatment.

Immunomodulatory Activity

The impact of red berries methanol extract on the proliferation response of peripheral blood mononuclear cells (PBMCs) from pigs, activated by phytohemagglutinin (PHA) and pokeweed mitogen (PWM), was studied. In PWM-activated cells, the extract enhanced proliferation, increasing with concentrations from 0.4 to 6 µg/mL. In PHA-activated cells, proliferation also increased at lower concentrations in this range, suggesting that red berries of *H. androsaemum* may modulate the immune system. However, the mechanisms remain unclear. At high doses (10 µg/mL), the extract elicited an inhibitory/cytotoxic reaction resulting in complete cell death [1]. Additionally, the extract modulated cytokine production by PBMCs [4].

DNA Protective Activity

Hydrogen peroxide (H_2O_2) is a major reactive oxygen species (ROS) responsible for DNA damage, primarily through conversion into hydroxyl radicals via the Fenton reaction. These radicals are highly reactive with biomolecules such as DNA, causing strand breaks. The protective effect of *H. androsaemum* water extract against H_2O_2-induced DNA damage was compared with extracts of *H. perforatum* and *H. undulatum*, quercetin, and rutin in HT29 colon cells. At a low concentration (1 µg/mL), *H. androsaemum* provided 40% protection, comparable to *H. undulatum*, quercetin, and rutin, but higher than *H. perforatum*. The antioxidant activity may be attributed to phenolic constituents such as quercetin and rutin. In this study, chlorogenic acid alone did not show significant protective effects. Against alkylating DNA damage, *H. androsaemum* showed minimal impact [56-58].

Conclusion

In this review, we have detailed the ethnobotanical uses, phytochemical composition, and biological activities of *Hypericum androsaemum*. This plant, traditionally used in the Mediterranean region, is known for its diuretic, hepatoprotective, antihypertensive, antihemorrhoidal, antidepressant, and skin-protective properties. Unlike *Hypericum perforatum*, the most well-known species in the genus for its antidepressant effects attributed to naphthodianthrone compounds, *H. androsaemum* lacks these compounds but still exhibits some antidepressant activity, suggesting the involvement of other bioactive constituents.

H. androsaemum is rich in a variety of compounds, including lignans, quinones, xanthones, polycyclic polyprenylated acylphloroglucinols (PPAPs), flavonoids, and triterpenoids. Extracts from this plant have demonstrated significant radical scavenging activity, although its hepatoprotective effects have not been conclusively supported. The fruits of *H. androsaemum* have shown cytotoxic activity against colon carcinoma, breast adenocarcinoma, and malignant melanoma cell lines, though the results against other cell lines were less promising. The plant also exhibits biocidal activity against certain bacteria, fungi, nematodes, mollusks, and insects, although the number of studies is limited, and some findings are inconsistent.

A particularly comprehensive study highlighted the plant's potential for treating skin conditions due to its ability to promote fibroblast proliferation and migration, inhibit collagenase and tyrosinase, modulate the immune system, and protect against UV damage and APPH-induced hemolysis. The absence of phototoxic hypericin in *H. androsaemum* further enhances its suitability for skin applications.

Various extracts of *H. androsaemum* have also shown immunomodulatory, DNA-protective, anti-glycation, antidepressant, and anti-inflammatory properties. However, the current body of research is still limited, and additional studies are necessary to confirm these effects and elucidate their underlying mechanisms.

Although there is no official pharmacopeial monograph for *H. androsaemum*, it is recommended that herbal preparations derived from this species be standardized for hyperforin content. This is important because potential risks associated with the oral administration of *Hypericum* species are linked to pharmacokinetic interactions caused by hyperforin. Given that the induction of metabolic enzymes by hyperforin is both dose- and time-dependent, the oral use of traditional *Hypericum* preparations should be limited to a duration of two weeks.

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