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BIOLOGICAL ACTIVITY OF *HYPERICUM PERFORATUM* L. (HYPERICACEAE): A REVIEW

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Hypericum perforatum L. (St. John's wort) is a medicinal plant that has been intensively studied by clinicians, pharmacologists, and chemists. It has resulted in the publication of both original articles and a number of reviews devoted to the general spectrum of the biological activity of its extracts and the separate chemical components of this species. Unlike many other known medicinal plants, the pharmacological study of which is accompanied by the establishment of new (or rediscovered) structures of chemical compounds, the dynamics of the present study of *H. perforatum* is mostly associated with a detailed study of the mechanisms of its therapeutic effect and less with the search for new components.
The aim of this work is to review and analyze the data on the biological activity of extracts and individual compounds of *Hypericum perforatum* L. (Hypericaceae), or St. John's wort, published in the scientific literature over the past 10 years.
Materials and methods. To collect and analyze the information, such electronic databases as PubMed, Scopus, Web of Science, Google Scholar, and other available resources have been used. The following keywords and word combinations were used for search in the databases for 2010–2020: "*Hypericum perforatum*", "St. John's wort", "the biological activity of St. John's wort", "hypericin", "hyperforin".
Results. The review provides information on antidepressant, neuroprotective, nootropic, anxiolytic activity, antibacterial, cytotoxic, anti-inflammatory properties, analgesic, hypoglycaemic effects, and other types of activity of *H. perforatum* extracts, as well as individual compounds (hypericin, hyperforin, amentoflavone, and others) isolated from this species. It is well known that the secondary metabolites of St. John's wort are naphthodianthrons, flavonoids and other phenolic compounds, several classes of lipophilic substances including phloroglucinol derivatives and terpenoids. Apart from extracts and their fractions, the biological activity of photoreactive naphthodianthrone hypericin and hyperforin (a phloroglucinol derivative) has been studied in detail.
This review provides an analysis of published data from 2010 to 2020 on the biological activity of St. John's wort. At the present time *H. perforatum* is primarily well-known for its antidepressant-like properties, which are confirmed by numerous pharmacological studies and clinical trials. Still there is no consensus on the effective treatment of severe or even moderate depression with St. John's wort. This review also provides information on the neuroprotective, nootropic, antiepileptic, anxiolytic, antimicrobial, antiviral, antiprotozoal, antitumor, cytotoxic, analgesic, anti-inflammatory and other effects of *H. perforatum* extracts, as well as its individual compounds.
Conclusion. Despite the popularity of *H. perforatum* as a plant with an antidepressant-like activity, intensive research work continues to be carried out to elucidate the molecular mechanisms of the actions of extracts and individual compounds in disorders of the nervous system. Studying its antibacterial, antiviral, and cytotoxic activity may also open up some great prospects, along with determining the possibility of using St. John's wort in metabolic disorders, genitourinary disorders, and other fields of medicine.
Keywords: St. John's wort; antidepressant; neuroprotective; nootropic; anxiolytic; antibacterial; cytotoxic; hypoglycaemic activity; hypericin; hyperforin; amentoflavone
Abbreviations: ROI – reactive oxygen intermediate; GABA – γ-aminobutyric acid; K562 – K-lines of acute erythroid leucosis; MAO-A – monoaminooxidase A; cAMP – cyclic adenosine monophosphate; CNS – central nervous system; A375 – human melanoma cell line; A375, 501mel – unpigmented melanoma cell lines; ADAMTS8, ADAMTS9 – a disintegrin-like and metalloprotease with thrombospondin type 1 motif 8, 9; BDNF – brain-derived neurotrophic factor; CaMK-IV – calcium/calmodulin-dependent protein kinase; cAMP – cyclic adenosine monophosphate; CLL – chronic lymphocytic leukemia cell line; COX – cyclooxygenases; CREB – cAMP response element-binding protein; CUMS – chronic unpredictable mild stress; CXCL9, CXCL10,

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– C-X-C motif chemokine; CYP3a CYP2c – cytochromes; D273 – medulloblastoma cell line; GABA – γ-aminobutyric acid; HT-29 – colon adenocarcinoma cell line; HT22 – immortalised mouse hippocampal neuronal cell line; iNOS – inducible nitric oxide synthase; JAK1 – janus kinase 1; JEG-3 – choriocarcinoma cell line; K562 – acute erythroid leukemia cell line; MAO-A – monoamine oxidase A; MAPK – mitogen-activated protein kinase; MCF-7 – human breast cancer cell line; MEK – mitogen-activated protein kinase kinase; MG-63 osteosarcoma cell line; NGF – nerve growth factor; NMDAR – N-methyl-D-aspartate receptor; PC12 – pheochromocytoma cell line; PGE_2 – prostaglandin E2; PI3K – phosphatidylinositol 3-kinase; PKB/Akt – protein kinase; RINm5F – insulinoma cell line; SCC – human squamous carcinoma cell line; SH-SY5Y – neuroblastoma cell line; TNFα – tumor necrosis factor α; TrkB – tropomyosin-related kinase B; TRPM2, TRPV1, TRPC6 – transient receptor potential cation channel; U937 – human acute myeloid leukemia cell line; UCT Mel-1 – pigmented melanoma cell line; β_1-AR – β_1-adrenergic receptors.

БИОЛОГИЧЕСКАЯ АКТИВНОСТЬ *HYPERICUM PERFORATUM* L. (HYPERICACEAE): ОБЗОР

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Hypericum perforatum L. (зверобой продырявленный) является лекарственным растением, которое в последнее время интенсивно изучается клиницистами, фармакологами и химиками. Результатами этого являются публикации как оригинальных статей, так и ряда обзоров, посвященных спектру биологической активности экстрактов и отдельных химических компонентов этого вида. В отличие от многих других известных лекарственных растений, фармакологическое изучение которых сопровождается установлением структур новых (или вновь обнаруженных) химических соединений, динамика современного изучения *H. perforatum* по большей части связана с детальным изучением механизмов его терапевтического действия и, в меньшей степени, с поиском новых компонентов.

Цель: обзор сведений по биологической активности экстрактов и отдельных компонентов *Hypericum perforatum* L. (Hypericaceae) – зверобоя продырявленного, опубликованных в научной литературе за последние 10 лет.

Материалы и методы. Для сбора и анализа сведений использовали электронные базы данных PubMed, Scopus, Web of Science, Google Scholar и др. доступные ресурсы. Поиск в базах данных производился по публикациям за 2010–2020 гг. по таким ключевым словам, как: *Hypericum perforatum*, зверобой продырявленный, St. John's wort, биологическая активность зверобоя.

Результаты. В обзоре представлены сведения об антидепрессивной, нейропротекторной, ноотропной, анксиолитической активности, антибактериальным, цитотоксическим, противовоспалительным свойствам, анальгезирующем, гипогликемическом действии, а также других видах активности экстрактов *H. perforatum* и индивидуальных соединений (гиперицина, гиперфорина, аментофлавона и др.), выделенных из этого вида. Как известно, пул вторичных метаболитов этого вида включает нафтодиантроны, флавоноиды и другие фенольные соединения, несколько классов липофильных веществ, в том числе производных флороглюцина и терпеноиды. При этом наиболее подробно (помимо экстрактов и их фракций) изучалась биологическая активность фотореактивного нафтодиантрона гиперицина и гиперфорина – производного флороглюцина. Данный обзор посвящен анализу сведений по биологической активности зверобоя продыявленного, опубликованных в литературе с 2010 по 2020 годы. В настоящее время популярность *H. perforatum* связана прежде всего с его антидепрессивными свойствами, которые подтверждены многочисленными доклиническими исследованиями и клиническими испытаниями, хотя до сих пор нет единого мнения о возможности эффективности использования зверобоя для лечения как тяжелой, так и даже умеренной депрессии. Кроме того, в данном обзоре приведены сведения о нейропротекторной, ноотропной, противоэпилептической, анксиолитической, антибактериальной, антивирусной, противопротозойной активности, противоопухолевых, цитотоксических, анальгезирующих, противовоспалительных и других свойств экстрактов и индивидуальных компонентов этого вида.

Заключение. Несмотря на известность *H. perforatum,* зверобоя продырявленного, как растения с антидепрессивной активностью, продолжаются интенсивные исследования, направленные на выяснение молекулярных механизмов действия экстрактов и индивидуальных соединений при патологиях нервной системы. Кроме этого, весьма перспек-

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тивными могут стать исследования его антибактериальной, антивирусной, цитотоксической активности, наряду с определением возможности применения з. продырявленного при нарушениях обмена веществ, функций мочеполовой системы и в других областях медицины.

Ключевые слова: зверобой продырявленный; *H. perforatum*; антидепрессивная активность; нейропротекторная активность; ноотропная активность; анксиолитическая активность; антибактериальная активность; цитотоксическая активность; гипогликемическая активность; гиперицин; гиперфорин; аментофлавон

Список сокращений: АФК – активные формы кислорода; ГАМК – γ-аминомасляная кислота; К562 – клетки линии К562 острого эритроидного лейкоза; МАО-А – моноаминооксидаза А; цАМФ – циклический аденозинмонофосфат; ЦНС – центральная нервная система; А375 и 501mel – клеточные линии непигментированных клеток меланомы А375 и 501mel; ADAMTS8 – дезинтегрин и металлопротеиназа с мотивом тромбоспондина 8; ADAMTS9 дезинтегрин и металлопротеиназа с мотивом тромбоспондина 9; BDNF – мозговой нейротрофический фактор; CaMK-IV – Ca^{2+}/кальмодулин-зависимая киназа IV типа; CLL – клетки линии CLL хронической лимфоцитарной лейкемии; COX2 – циклооксигеназа 2; CREB – фактор транскрипции CREB; D273 – клетки линии D273 медуллобластомы; HT-29 – клеточния линия HT-29 аденокарциномы толстой кишки; iNOS – индуцируемая NO-синтаза; JAK1 – янус-киназа 1; MAPK – митоген-активируемая протеинкиназа; MCF-7 – клетки линии MCF-7 рака молочной железы; MEK – киназа митоген-активируемой протеинкиназы; mPGES – микросомальная простагландинсинтаза; NMDA – N-метил-D-аспартатные рецепторы; PC12 – клетки феохромоцитомы PC12 ; PI3K – фосфатидилинозитол-3-киназа; PKB – протеинкиназа B; RINm5F – клетки линии RINm5F инсулиномы; SCC – клетки линии SCC чешуйчатой карциномы человека; TNFα – фактор некроза опухоли α; TrkB – тропомиозиновый тирозинкиназный рецептор B; TRPM2, TRPV1, TRPC6 – каналы транзиторного рецепторного потенциального катиона TRPM2, TRPV1, TRPC6; U937 – клетки линии U937 острой миелоидной лейкемии; UCT Mel-1 – клеточная линия UCT Mel-1 пигментированных клеток меланомы; β_1-АР – β_1-адренорецептор

INTRODUCTION

Despite the fact that *Hypericum perforatum* L. (St John's wort) has been known for its medicinal properties for more than 2000 years, it has not yet lost its popularity and continues to be studied intensively by clinicians, pharmacologists, and chemists. The indicator of the active interest in *H. perforatum* is the number of reviews published over the last decade. They are devoted to both the general biological activity profile of its extracts and individual chemical components, as well as to specific types of activity, which are considered in the corresponding sections of this article.

Unlike many other medicinal plants, pharmacological studies of which are accompanied by the determination of the structures of certain new (or rediscovered) chemical compounds, modern research of *H. perforatum* is more focused on the mechanisms of its therapeutic action, and less on the identification of new components.

It is well known that among the secondary metabolites of St. John's wort, there are naphthodianthrons, flavonoids and other phenolic compounds, several classes of lipophilic substances including phloroglucinol derivatives and terpenoids. Apart from extracts and their fractions, the biological activity of hypericin, a photoreactive naphthodianthrone, and hyperforin — a phloroglucinol derivative, have been studied in most detail [1–5].

Today, *H. perforatum* is known primarily for its antidepressant-like properties, which have been confirmed by numerous preclinical studies and clinical trials. Still, there is no consensus on the effectiveness of St. John's wort for severe or at least moderate depression (e.g. [2]).

And yet, the aforementioned beneficial properties of *H. perforatum*, as well as those yet unknown, continue to be studied with unceasing regularity, in different models and within different approaches. A brief (but by no means exhaustive) summary of such studies conducted over the past decade, is presented in this review.

THE AIM of this work is to review and analyze the data on the biological activity of extracts and individual components of *Hypericum perforatum* L. (Hypericaceae), or St. John's wort, published in the scientific literature over the past 10 years.

MATERIALS AND METHODS

To collect and analyze the information, electronic databases PubMed, Scopus, Web of Science, Google Scholar, and other available resources have been used. The following keywords and word combinations were used for search in the databases for 2010-2020: "*Hypericum perforatum*", "St. John's wort", "the biological activity of St. John's wort", "hypericin", "hyperforin".

RESULTS AND DISCUSSION

Antidepressant activity

Despite St. John's wort being a popular "mild" treatment choice for depression, its mechanism of action is not entirely known yet. According to current understanding, among its most active components are the naphthodianthrone hypericin, the phloroglucinol derivatives hyperforin and adhyperforin, the biflavonoid amentoflavone, and other flavonoids [6–13].

According to a systematic review and a meta-analysis, which included 27 clinical trials, St. John's wort is as effective in the patients with mild-to-moderate depression as are some of the most common synthetic antidepressants, at the same time being better tolerated [14–16]. *H. perforatum* is most effective in patients with mild and moderate depression [15–18], and in those experiencing pronounced somatization and gastrointestinal symptoms [19].

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Standardized *H. perforatum* extracts WS 5572, LI 160, WS 5570, ZE 117 were found to be as effective for mild depression as sertraline and imipramine [20, 21]. In moderate depression, *H. perforatum* did not differ in effectiveness from citalopram [22] while surpassing paroxetine [23]. According to a retrospective observational study, IperiPlex®, a multi-fractionated *H. perforatum* extract, was significantly more effective in the patients with moderate depression than Nervaxon®, a mono-fractionated extract [24]. However, *H. perforatum* effectiveness in patients with moderate and severe depression remains somewhat unclear [25, 26].

A multicenter observational study showed the drugs Helarium® and Helarium-425®, both containing extracts of *H. perforatum,* to be well-tolerated by patients with mild to moderate depression [27]. However, *H. perforatum* treatment was associated with a greater frequency of some specific adverse events, including damage to the nervous system, reproductive organs, eyes, ears, liver, and kidneys [28]. A case of psychosis has been reported in a patient who self-administered *H. perforatum* as a herbal infusion [29].

H. perforatum extract potentiated yohimbine toxicity, and exhibited maximal antidepressive activity at 90 mg/kg [14]. Administered over time, both *H. perforatum* ethanolic extract and fluoxetine were found to affect hippocampal and hypothalamic gene expression in chronically stressed rats. Among those affected were genes coding for a number of biomolecules involved in neuroinflammatory and oxidative stress pathways, and some of those associated with Alzheimer's disease [30].

In 2018, T. Herraiz et al. showed that in various dosage forms, *H. perforatum* inhibited monoamine oxidase A (MAO-A). Of all the identified plant constituents, quercetin (IC_{50}= 3.4 µg/ml) and its glycosides were found to be the most active; hypericin (IC_{50} = 17.9 µg/ml) did not contribute significantly to the overall effect of the preparations, and hyperforin failed to show any activity throughout the studied concentration range. According to the authors, taking into account the average content of active ingredients in total preparations with *H. perforatum*, the observed MAO-A inhibition was most likely an additive effect [31].

When compared to venlafaxine, a serotonin and norepinephrine reuptake inhibitor, hypericin decreased blood corticosterone levels, prevented weight loss and anorexia, reduced anhedonia, and stimulated exploratory behaviour in rats with a chronic unpredictable mild stress (CUMS). Moreover, those effects had a shorter onset in the hypericin-treated group than in the venlafaxine-treated one. At the same time, hypericin affected the metabolism of norepinephrine, serotonin, and excitatory amino acids (glutamate and glutamine) [12]. Hypericin also inhibited calcium ion influx into hippocampal neurons, thus increasing an action potential duration, which could possibly play a role in enhancing a synaptic efficiency [32].

Pretreatment of glioblastoma cells with hyperforin and hyperoside hindered lateral mobility of β_1-adrenergic receptors (β_1-AR) and caused their internalization. The two compounds reduced cyclic adenosine monophosphate (cAMP) formation by 10% and 15%, respectively, and by 23% and 15% under subsequent cell stimulation with 5 µM dobutamine. Similar effects were observed when cells were pretreated with desipramine, a tricyclic antidepressant [7]. *H. perforatum* extract and hyperforin were found to increase presynaptic calcium concentrations and thus stimulate the release of the excitatory neurotransmitter glutamate [33].

B. Pochwat et al. found that hyperforin potentiated antidepressant-like activity of lanicemine, a N-methyl-D-aspartate receptor (NMDAR) antagonist, in chronic corticosterone-treated mice as well as in healthy controls. A combination of lanicemine and hyperforin increased the expression of synapsin I, a subunit of glutamate receptor A_1, and neurotrophin BDNF (brain-derived neurotrophic factor) in frontal cortical neurons. Hyperforin also attenuated cognitive dysfunction caused by dizocilpine, a NMDAR antagonist having marked dissociative and psychedelic properties. Nonetheless, 0.3–10 µm hyperforin did not affect NMDAR electrical activity *in vitro* [13].

Much less is known about adhyperforin than about its parent compound, hyperforin. However, adhyperforin has also been shown to exert an antidepressant-like activity, stimulate exploratory behaviour, and reduce anhedonia and hypodynamia in rodents. It suppressed norepinephrine, serotonin and dopamine reuptake *in vitro*, and, just like hyperforin, antagonized reserpine-induced effects *in vivo* [8, 34].

Neuroprotective activities

An ethanolic extract of *H. perforatum* containing 6.0% of hyperforin stimulated neurite outgrowth in HT22 hippocampal cells, increased their resistance to glutamate toxicity, and inhibited the release of tumor necrosis factor α (TNFα) from macrophages [35].

Pretreatment of PC12 pheochromocytoma cells with an *H. perforatum* extract increased their viability at toxic concentrations of hydrogen peroxide, and prevented DNA fragmentation [36]. Another *H. perforatum* extract normalized lateral mobility of integral membrane proteins and phospholipids in glioblastoma cells, which made a more efficient transmembrane signal transduction possible [37]. Ethyl acetate, water, and methanolic extracts of *H. perforatum* inhibited acetyl- and butyrylcholinesterase; ethyl acetate and water extracts also inhibited tyrosinase [38].

An extract of *H. perforatum* reduced the severity of oxidative stress in leukocytes obtained from patients with multiple sclerosis. Cell apoptosis was largely prevented through the activation of antioxidant systems and normalization of intracellular calcium levels [39]. A similar effect associated with the blockade of calcium channels by *H. perforatum* was also observed in rat

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dorsal root ganglion neurons [40]. Later, some of the active constituents of *H. perforatum* were found to inhibit TRPM2 and TRPV1 channels, which mediate calcium ion influx under oxidative stress conditions [41].

A hyperforin-enriched (6.0%) extract (4 mg/kg/d×45 d) effectively prevented degeneration of nigral neurons induced in rats by a chronic exposure to rotenone. Quite on the contrary, an extract containing only 0.2% hyperforin and pure quercetin both exhibited significantly lower activity when administered by the same route and at the same doses [42]. The rats treated with an ethanolic extract of *H. perforatum* (200 mg/kg/d) for 1 week before and 1 week after the administration of 6-hydroxydopamine showed an increase in survival rates of nigral neurons, as well as an attenuation of astrogliosis, inflammation, oxidative stress, and motor dysfunction as compared to control animals [43]. Both St. John's wort extract and pure hyperforin alleviated the symptoms of experimental autoimmune encephalomyelitis, a common model of multiple sclerosis, in mice [44, 45]. An ethanolic extract of St. John's wort also prevented apoptosis of neurons and attenuated oxaliplatin-induced neurotoxicity in rats [46].

In the study by S. Valvassori et al., an *H. perforatum* extract (300 mg/kg /d × 28 d) significantly impaired memory acquisition and object recognition, and decreased the levels of the transcription factors BDNF and NGF (nerve growth factor) in rat hippocampi [47].

In an *ex vivo* experiment in isolated hippocampal neurons, hyperforin (0.3 μM, 24 h) promoted the formation of stubby dendritic spines and, at the same time, decreased the proportion of thin spines [48]. Interestingly, similar alterations in spine morphology have been observed for classical antidepressant agents such as fluoxetine [49], imipramine, and rolipram [50], but in those cases, they had a significantly slower onset, and most probably differed in nature [48].

Hyperforin activated MEK (mitogen-activated protein kinase), MAPK (mitogen-activated protein kinase), phosphatidylinositol 3-kinase (PI3K), protein kinase B (PKB/Akt), and calcium/calmodulin-dependent protein kinase (CaMK-IV) in PC-12 pheochromocytoma cells and hippocampal neurons [51]. These changes culminated in the phosphorylation and activation of the transcription factor CREB (cAMP response element-binding protein), which is considered to be a promising therapeutic target for the treatment of Alzheimer's disease [52–54]. Moreover, the therapeutic effect of *H. perforatum* in Alzheimer's disease was seemingly independent of hyperforin concentration in the preparation [55]. Hyperforin was confirmed to exert neuroprotective effects against aluminum maltolate-induced toxicity in PC12 and SH-SY5Y cells [56].

Hyperforin stimulated CREB phosphorylation, induced TRPC6 calcium channel and TrkB BDNF receptor expression in embryonic mouse cortical neurons [57]. The extract of *H. perforatum* reduced a β-amyloid accumulation and increased levels of P-glycoprotein in the brain tissue of transgenic mice with Alzheimer's disease. However, another study found an *H. perforatum* extract, hyperforin, and high concentrations of quercetin to inhibit P-glycoprotein activity in brain capillary endothelial cells [59]. A methanolic extract of *H. perforatum* inhibited acetylcholinesterase and reduced glutamate levels, at the same time potentiating noradrenergic and dopaminergic neurotransmission in an aluminum chloride-induced rat model of Alzheimer's disease. The extract caused a decrease in β-amyloid deposition rates and ameliorated oxidative stress in treatment groups [60]. A 28 days-long *H. perforatum* treatment course inhibited neuroinflammation, lipid peroxidation, and lowered blood proinflammatory cytokines levels in rats subjected to mechanic sciatic nerve injury [61].

An intracerebroventricular administration of hyperforin to rats subjected to middle cerebral artery occlusion, significantly reduced infarct volume and post-stroke neurological deficit. Hyperforin inhibited the calpain-mediated TRPC6 channel degradation, thus maintaining normal CREB activity and, ultimately, increasing neuron viability following ischemia [62].

TRPC6 activation is thought to be a non-essential or, at the very least, not the only mechanism of a hyperforin action [9, 34]. For instance, a complete absence of TRPC6 had no effect on inward membrane ion currents in microglial cells treated with a hyperforin solution. Its molecule being highly lipophilic, and its properties depending heavily on pH of the medium, it was suggested that hyperforin acted as a protonophore and induced a transmembrane proton transfer in a channel-independent fashion [34]. However, in an *in vivo* experiment in mice, its neurotropic activity was blocked completely by a prior administration of either larixyl acetate or MK 2206, which inhibited TRPC6 and PKB, respectively [13].

Amentoflavone and hypericin are thought to have an opposite effect on a MAPK pathway activity compared to hyperforin [63–65]. Amentoflavone protected HT22 hippocampal neurons against glutamate-induced excitotoxic injury. Besides maintaining the activity of some of the most important antioxidant enzymes and inhibiting reactive oxygen species generation, it inhibited MAPK phosphorylation [66].

Amentoflavone has been shown to exert a direct effect on cholinergic neurotransmission in the central nervous system. It significantly attenuated scopolamine-induced retrograde amnesia through inhibition of acetylcholinesterase and enhancement of antioxidant enzymes activity, thus perpetuating long-term spatial memory [67].

Nootropic activity

A 2016 meta-analysis confirmed *H. perforatum* to possess a significant nootropic activity independent of its antidepressant-like activity. The authors suggested

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that the modulation of 5-HT_2 serotonin receptor activity, dopaminergic, glutamatergic, and γ-aminobutyric acid (GABA)-mediated neurotransmission was among the possible mechanisms of *H. perforatum* nootropic action [68]. Long-term *H. perforatum* treatment has been shown to inhibit the release of adrenocorticotropin and, as a result, that of the glucocorticoid corticosterone, which is the main hormonal mediator of chronic stress response in rodents [68, 69]. An *H. perforatum* extract (125, 250 or 500 mg/kg/d × 30 d) prevented an increase in corticosterone and TNF-α levels in blood and hippocampus in bilateral ovariectomized rats [70].

The nootropic effects of *H. perforatum* preparations have been confirmed experimentally using acute [71] and chronic restraint stress models [72], and a model of cognitive deficit associated with diabetes mellitus [73].

H. perforatum preparations have been demonstrated to have a beneficial effect on neuronal synaptic plasticity in animal [74, 75] and human studies [76]. A single dose of 250 mg of *H. perforatum* tabletted dry extract (Remotiv®) improved short-term verbal and spatial memory in healthy volunteers. Quite surprisingly, no nootropic effect was observed at the dose of 500 mg, although both doses improved the patients' mood and emotional stability. Similarities to and differences from some other neurotropic agents such as citalopram, bromocriptine, and sulpiride, as well as the inverse dose-dependency of *H. perforatum* effects suggest that its primary mechanism of action could involve the augmentation of dopaminergic transmission [77].

The effectiveness of *H. perforatum* for the treatment of autism spectrum disorder is limited. St. John's wort modestly improved irritability, stereotypy and abnormal speech patterns, while clinician ratings on several symptom assessment scales remained unchanged [78].

Antiepileptic activity

Amentoflavone exhibited antiepileptic properties in a number of *in vitro* and *in vivo* studies. It attenuated oxidative stress, inhibited neuroinflammation, and increased GABA binding affinity to $GABA_A$ receptors [79–81]. An ether extract of *H. perforatum* lowered the seizure threshold and increased the after-discharge duration, while *n*-butanolic and water extracts, on the contrary, inhibited epileptogenesis [82]. A methanolic extract of *H. perforatum* reduced seizure duration and mortality in a mouse model of picrotoxin-induced epilepsy [83].

Anxiolytic activity

Anxiolytic properties of *H. perforatum* are related to its nootropic, neuroprotective and antidepressant-like kinds of activity, and are thought to be mediated by its effects on monoaminergic transmission and neuroinflammatory processes [71, 74].

The anxiolytic effect of amentoflavone (25 mg/kg), observed in mice following a single administration, was reduced by pretreatment with flumazenil, a benzodiazepine receptor antagonist. This fact suggested that amentoflavone exerted its anxiolytic effect through the interaction with the benzodiazepine-binding site of the $GABA_A$ receptor [84]. This mechanism of action was subsequently confirmed by radioligand binding assays [85].

Crupi et al. revealed that three-week treatment with an *H. perforatum* methanolic extract decreased anxiety in mice with chronic corticosterone-induced stress [74]. Extract-treated (50 or 100 mg/kg/d × 5 d) mice exhibited higher levels of exploratory activity and were less anxious following six hours of acute restraint stress, although those parameters still fell outside normal ranges [71]. An *H. perforatum* extract (100 or 200 mg/kg/d × 14 d) ameliorated anxiety and depression in streptozotocin-induced type II diabetic rats [86].

Antimicrobial, antiviral and antiprotozoal activity

Antibacterial activity of *H. perforatum* has been reviewed by Z. Saddiqe et al. in 2010 [87]. The antibacterial activity of individual compounds and extracts of St. John's wort is somewhat unclear. Aerial parts macerated with olive oil showed little overall activity, and only a few samples were active against *Trypanosoma brucei rhodesiense* and *Staphylococcus aureus* [88]; hyperforin (but not hypericin) also moderately inhibited *Staphylococcus aureus* growth [89]. The aqueous fraction of an ethanolic extract of St. John's wort suppressed *Streptococcus sobrinus* and *Lactobacillus plantarum* growth [90], and an alcoholic extract and hypericin were active against *Lactobacillus acidophilus*, allowing to consider them as potential oral disinfectants [91]. Photoactivated hypericin inhibited *Candida albicans*, *C. parapsilosis, C. krusei* [92], and *Staphylococcus aureus* growth, but did not affect that of *Escherichia coli* [93]. Hyperforin and a methanolic extract of the aerial parts of the plant were active against *Mycobacterium JLS*, although hypericin and pseudohypericin were not [94]. An ethyl acetate extract of *H. perforatum* exhibited antiviral activity against infectious bronchitis virus *in vitro* and *in vivo* (IBV strain M41) [95], human influenza virus A/PR/8/34 H1N1 [96], influenza A virus [97], and hepatitis B virus [98].

Antitumor and cytotoxic properties

An overview summarizing existing knowledge on the anticancer activity of *Hypericum* species was published in 2017 [99]. It was established that ultraviolet radiation increased the antiproliferative activity of a water/alcohol extract in human melanoma A375 cell line [100]. Investigations are underway to assess the cytotoxic activity of *H. perforatum* components in photodynamic therapy. For instance, hyperforin and aristofolin (a synthetic derivative of hyperforin) induced apoptosis of HT-29 colon adenocarcinoma cells subjected to hypericin-mediated photodynamic therapy [101], and death of both unpigmented (A375 and 501mel) and pigmented (UCT

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Mel-1) melanoma cells [102][1]. Photoactivated hypericin decreased the viability of RINm5F insulinoma cells, human squamous carcinoma cells (SCC) [104], D273 medulloblastoma cells [105], and was effective against anaplastic thyroid cancer [106]. A flower extract inhibited growth and induced apoptosis of K562 (acute erythroid leukemia) cells [107], an ethanolic extract blocked proliferation and induced apoptosis of MCF-7 human breast cancer cells [108], and hyperforin induced death of CLL (chronic lymphocytic leukemia) cells *ex vivo* [109]. Hypericin exerted a cytotoxic effect on MCF-7 cells [110], promoted expression of genes coding for metalloproteinase family enzymes ADAMTS9 and ADAMTS8 having anti-angiogenic and antitumor properties in MCF-7 cells [111]. Hyperforin induced apoptosis of U937 (human acute myeloid leukemia) cells line [112]. An essential oil showed anti-angiogenic properties [113].

Analgesic, anti-inflammatory and wound-healing properties

There has been published a number of reviews focused on the anti-inflammatory and analgesic properties of *H. perforatum* extracts and their components [114–118]. A dry extract relieved neuropathic pain in an experimental study [119]. Hypericin inhibited the pro-inflammatory enzyme janus kinase 1 (JAK1) *in silico,* which could explain its anti-inflammatory properties [120].

Hyperforin inhibited the activity of cyclooxygenases (COX) 1 and 2 and microsomal prostaglandin synthase PGE_2, which play key roles in inflammation and tumorigenesis [121]. Over the past decade, the investigations of anti-inflammatory properties of the four-component fraction of *H. perforatum* ethanolic extract containing amentoflavone, quercetin, chlorogenic acid and pseudohypericin, have been continued [122, 123]. The extract was found to be devoid of anti-inflammatory activity, in contrast with the four compounds [124]. *H. perforatum* flowering tops extract suppressed the expression of proinflammatory factors and stimulated that of anti-inflammatory ones in cultured adipocytes [125].

An extract facilitated wound healing properties in a clinical trial [126], and was effective for the treatment of psoriasis, lowering TNFα levels in dermis, endothelial, and dendrite cells [127]. An ethanolic extract prevented lipid peroxidation in neutrophils of patients with Behcet's syndrome [128]. An oil extract was effective for the prevention and treatment of pressure sores [129]. Wound-healing properties of *H. perforatum* extracts were confirmed in different models [130–133] including diabetic animals [134–136]. An oil extract prevented the narrowing of the oesophageal lumen caused by burn injuries [137], and had anti-inflammatory, anti-angiogenic, and anti-fibroblastic effects when applied after corneal alkali burns [138]. Hyperforin reduced the migration of fibroblasts in 2D and 3D models of artificial skin and was proposed for the treatment of hypertrophic scars [139].

Hypolipidaemic and hypoglycaemic properties

Hypolipidaemic and hypoglycaemic properties have been discovered for extracts of the aerial parts of *H. perforatum* [141–143]. A hydroalcoholic (50%) extract of the whole plant at the doses of 100 and 200 mg/kg of body weight per day for 15 days exhibited hypocholesterolaemic properties [144], and similar effects were observed for an aqueous extract of the aerial parts at the dose of 300 mg/kg for 60 days [145]. A methanolic extract and hyperforin prevented pancreatic β-cells from damage by the cytokines iNOS, CXCL9, CXCL10, and COX2, which is associated with the development of type I diabetes [146]. It was found that excessive intake of *H. perforatum* flower extract, hypericin, and hyperforin could aggravate diabetes and obesity by inhibiting the differentiation of preadipocytes and inducing insulin resistance in mature fat cells [147].

Effects of *H. perforatum* in genitourinary system disorders

A powder of shoots at the dose of 200 mg/kg (8 weeks) in diabetic nephropathy showed a nephroprotective effect [147]. A methanolic extract of the aerial parts of *H. perforatum*, hypericin, and hyperforin exhibited spasmolytic activity and modulated detrusor contractile activity in isolated urinary bladder; for hypericin, this effect was associated with an increase in plasma membrane depolarization, and for hyperforin, with a stimulatory effect on the cholinergic system [149]. A hydroalcoholic extract of leaves reduced the size and number of ethylene glycol-induced renal calculi [150].

Clinical trials found out that a powder of St. John's wort given at the doses of 270–330 μg for 2 months reduced hot flashes, menopausal symptoms, and depression [151], and the extract was effective for the treatment of premenstrual syndrome [152]. In an *in vitro* experiment, the extract (25 μg/mL) and hypericin (7.5 and 75 ng/mL) increased calcium concentration in JEG-3 placental cells [153]. The extract intake (100 mg/kg and 300 mg/kg) from mating till delivery prolonged foetal development and damaged foetal liver due to oxidative stress [154]; at the same doses, the extract worsened ovarian function and decreased fertility [155].

Effects of *H. perforatum* in maxillofacial injuries

An aqueous extract of the aerial parts activated a bone tissue regeneration in the orthopaedically expanded premaxillary suture, which is performed in orthognathic surgery [156]. Another experiment proved a standardized methanolic extract to restore mandible bone tissue in a stress model [157]; an ethanolic extract activated dental pulp regeneration [158]), and an oil extract improved bone healing after xenograft−implantation [159].

[1] It was reported that the cytotoxicity of photodynamic hypericin was higher for amelanotic A375 melanoma cells in comparison with pigmented Mel-1 cells; in this regard, melanin was suggested to play a role in the chemoresistance of melanoma cells (Sharma, Davids, 2012b).

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Other effects

Several *H. perforatum* extracts prevented acetaminophen-induced liver injury [160, 161], a petroleum ether leaf extract had protective effects in a hepatic ischaemia-reperfusion model [162], and another extract accelerated hepatic clearance of technetium-99 [163]. Certain fractions of a water/ethanol extract of the aerial parts of *H. perforatum* had spasmolytic, bronchodilator, vasorelaxant and cardiotropic activities [164]; *H. perforatum* polysaccharides and a methanolic seed extract showed antioxidant properties [165, 166]. It is assumed that the antioxidant properties underly the photoprotective and anti-inflammatory effects of hyperforin on skin tissues [167]. At the doses of 250 and 500 mg/kg, a *H. perforatum* dry extract reduced binge eating episode frequency [168]. A leaf extract had antimutagenic properties [169]; the effects of hyperforin were described as antigenotoxic [170] and DNA-protective [171] in different *in vitro* models. An ethanolic extract of *H. perforatum* stimulated human osteoblast-like MG-63 cell proliferation in osteoporosis induced by ovariectomy [172]. A hydroalcoholic extract (110 mg/kg for 2 weeks) enhanced cellular immunity [173], and a methanolic extract of the aerial parts, dissolved in olive oil, prevented the development of myringosclerosis after myringotomy [174]. The β-diketone 2,6,9-trimethyl-8-decene-3,5-dione, hyperforatins B, D, and F, 15-epi-hyperforatin D, and 32-epi-hyperforatin E inhibited an acetylcholinesterase activity [175, 176], and a methanolic extract stimulated hepatic and renal activities of the cytochromes CYP3a and CYP2c [177].

CONCLUSION

Despite the popularity of *H. perforatum* as a plant with an antidepressant-like activity, intensive research work continues to be carried out to elucidate the molecular mechanisms of the actions of extracts and individual compounds in disorders of the nervous system. Studying its antibacterial, antiviral, and cytotoxic activity may also open up some great prospects, along with determining the possibility of using St. John's wort in metabolic disorders, genitourinary disorders, and other fields of medicine.

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AUTHORS' CONTRIBUTION

A.L. Budantsev – writing Introduction and Antibacterial, antiviral, antiprotozoal activity, Antitumor and cytotoxic properties, Analgesic, anti-inflammatory and wound-healing properties, compiling the list of references; I.V. Varganova – compiling of Antibacterial, antiviral, antiprotozoal activity, Antitumor and cytotoxic properties, Analgesic, anti-inflammatory and wound healing properties, Hypolipidemic and hypoglycemic properties, other effects, translation of the text into English, compiling the list of references; V.A. Prikhodko – compiling of Antidepressant activity, Neuroprotective activity, Nootropic activity, Antiepileptic activity, Anxiolytic activity, Effects of *H. perforatum* in genitourinary system disorders, Effects of *H. perforatum* in maxillofacial injuries, translation of the text into English, compiling the list of references; S.V. Okovity – compiling of Antidepressant activity, Neuroprotective activity, Nootropic activity, Antiepileptic activity, Anxiolytic activity, Effects of *H. perforatum* in maxillofacial injuries, Effects of *H. perforatum* in maxillofacial injuries.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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