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A current update on phytochemistry, pharmacology and herb–drug interactions of *Hypericum perforatum*

Vinay S. Velingkar · Girdharilal L. Gupta · Namita B. Hegde

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Abstract *Hypericum perforatum* L. is an ethnomedicine with a popular remedial legacy; especially of antidepressant and wound healing properties. Rigorous preclinical and clinical research conducted in last sesqui-decade has revealed newer facets of its therapeutic activities against psychiatric, metabolic and neoplastic disorders. Most of such curative effects are imparted synergistically by hypericin, hyperforin and flavonoids; but their action mechanisms remain ambiguous. Concomitant administration of St. John's Wort formulation and cytochrome P450 substrate drug is limited by the episodes of herb–drug interactions; nevertheless, adverse drug reaction rate of *H. perforatum* remains only 2%. In present review, we aim to highlight the 'evidence-based' therapeutic potential of aforementioned phytopharmaceutical, which would accelerate the contemporary pharmaceutical development of this traditional phytomedicine.

Keywords Antidepressant · Flavonoids · Hyperforin · Hypericin · St. John's Wort

Abbreviations

CRF	Corticotropin-releasing factor
CYP	Cytochrome P450
HPAA	Hypothalamic–pituitary–adrenal axis
HYP	*Hypericum perforatum* L.
HYPE	*H. perforatum* extract
HYPEs	*H. perforatum* extracts
IC_{50}	Half maximal inhibitory concentration,
P-gp	P-glycoprotein
TRPPC	Transient receptor potential protein channel

V. S. Velingkar · G. L. Gupta · N. B. Hegde (✉)
Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM's NMIMS University, Mumbai, India
e-mail: hegde.namita@ymail.com

Introduction

Hypericum perforatum L. (HYP) is a forb indigenous to Europe, North Africa and Western Asia; but due to its cultivation as a medicinal or garden plant, it is now widespread to the temperate regions like Australia, India, New Zealand, South Africa and South America (Zouhar 2004). It is a perennial shrub that grows 1–3 feet tall and propagates by vegetative as well as sexual means. The prominent morphological features of HYP include tap root system, woody stems, rhizomes, runners, leaves with pellucid glands all over the lamina and cyme of yellow flowers, which develop into the seed-storing dehiscent capsules (Sheahan 2012; WHO 1999).

Although claimed a "noxious weed" in few regions (Sheahan 2012), HYP has been used as a salubrious herb since antiquity, precisely with a Greek origin. From the ancient as well as modern literature, its mention in several official herbal compendia and extensive use in the cure of psychiatric disorders like

depression, social phobia, obsessive-compulsiveness and somatization is evident (Clauson et al. 2008; Klemow et al. 2011; Sarris 2013). Therapeutics of HYP were known centuries ago, but its cytochrome P450 (CYP) and P-glycoprotein (P-gp) mediated herb–drug interactions were unknown (Greeson et al. 2001; Rahimi and Abdollahi 2012). The phytoconstituents of HYP include naphthodianthrones, phloroglucinols, flavonoids, xanthones, essential oils, phenolic acids and proanthrocyanidins (Patočka 2003). Various HYP formulations are available as over-the-counter drugs or dietary supplements in different countries (Brinckmann and Wollschlaeger 2003).

In this article, we discuss botany, phytochemistry, pharmacological activities and herb–drug interactions concentric to the phytopharmaceutical-HYP. Major content of this scrutiny comes from the research conducted in last sesqui-decade. This review aims to highlight the 'evidence-based' therapeutic potential of HYP, which would accelerate the contemporary pharmaceutical development of this traditional phytomedicine.

Botany

Almost 500 diverse species are identified in genus *Hypericum*, which can habitat anywhere in the world except for arid deserts, low altitude tropics and poles (Meseguer et al. 2013). Taxonomically HYP can be classified as Kingdom: Plantae; Subkingdom: Viridiplantae; Infrakingdom: Streptophyta; Superdivision: Embryophyta; Division: Tracheophyta; Subdivision: Spermatophytina; Class: Magnoliopsida; Superorder: Rosanae; Order: Malpighiales; Family: Hypericaceae; Genus: *Hypericum* L.; Species: *H. perforatum* L. (ITIS 1996). Synonyms of HYP include *H. perforatum* var. *veronense*, *H. perforatum* var. *microphyllum*, *H. perforatum* var. *angustifolium* and many more (The Plant List 2013). Other than St. John's Wort, Klamath weed, Goatweed, Tipton weed, Rosin-rose, etc. are the common names of HYP (Sheahan 2012).

The crude HYP drug chiefly comprises of green leaves, stems, flower buds and bloomed flowers. The leaves are oblong shaped, sessile and photosynthetic in nature. In a leaf held against light, laminal oil glands resemble transparent dots; giving it a perforated appearance. The stems are devoid of trichomes, grow upright and develop branching in upper shoot. The flowers are yellow coloured and contain floral whorls characteristic to Angiosperms (Grieve 1995). Predominant phytochemicals of HYP are synthesized and stored in dark/pale glands and secretory pockets in its aerial parts (Soelberg et al. 2007; WHO 1999; Zobayed et al. 2006).

Phytochemistry

The vital compounds imparting medicinal properties to *Hypericum* species include naphthodianthrones (e.g. hypericin and pseudohypericin), phloroglucinols (e.g. hyperforin) and flavonoids (e.g. quercetin, quercitrin, hyperoside and rutin) (Stojanovic et al. 2013). Chemical structures of such important actives are compiled in Fig. 1. Also, phytoconstituents of HYP are enlisted in Table 1. Besides the enlisted ones, few new moieties are also isolated from HYP by chromatography (Ma et al. 2012).

Hypericin and pseudohypericin accumulate inside the dark glands along leaf and petal margins, and their biosynthesis is hypothesised to follow the polyketide pathway. Emodin dianthrone is derived from emodin anthrone that plays a precursor in the presence of Hyp-1 enzyme. Oxidation of emodin dianthrone forms protohypericin, while oxidation of methyl group of protohypericin forms protopseudohypericin. Photoactivation of protohypericin and protopseudohypericin results into hypericin and pseudohypericin, respectively. Although the theory is accepted unanimously by researchers, it remains needful of enough supporting scientific evidences. Besides, characterization of polyketide synthases involved in this route is yet to be done (Karioti and Bilia 2010). In contrast to hypericin, hyperforin is primarily synthesized in pale glands, but might occur in minute quantities in dark glands also. Biosynthesis of hyperforin partly coincides with the non-mevalonate pathway of monoterpenes. Three dimethylallyl diphosphate molecules and a single molecule of geranyl diphosphate link up with phloroglucinol moiety, and on ring closure give hyperforin (Soelberg et al. 2007). The isoprenoid units and phloroglucinol moieties are produced from deoxyxylulose phosphate and polyketide pathways, respectively (Adam et al. 2002). Depending upon the set of enzymes active in HYP, different flavonoids are

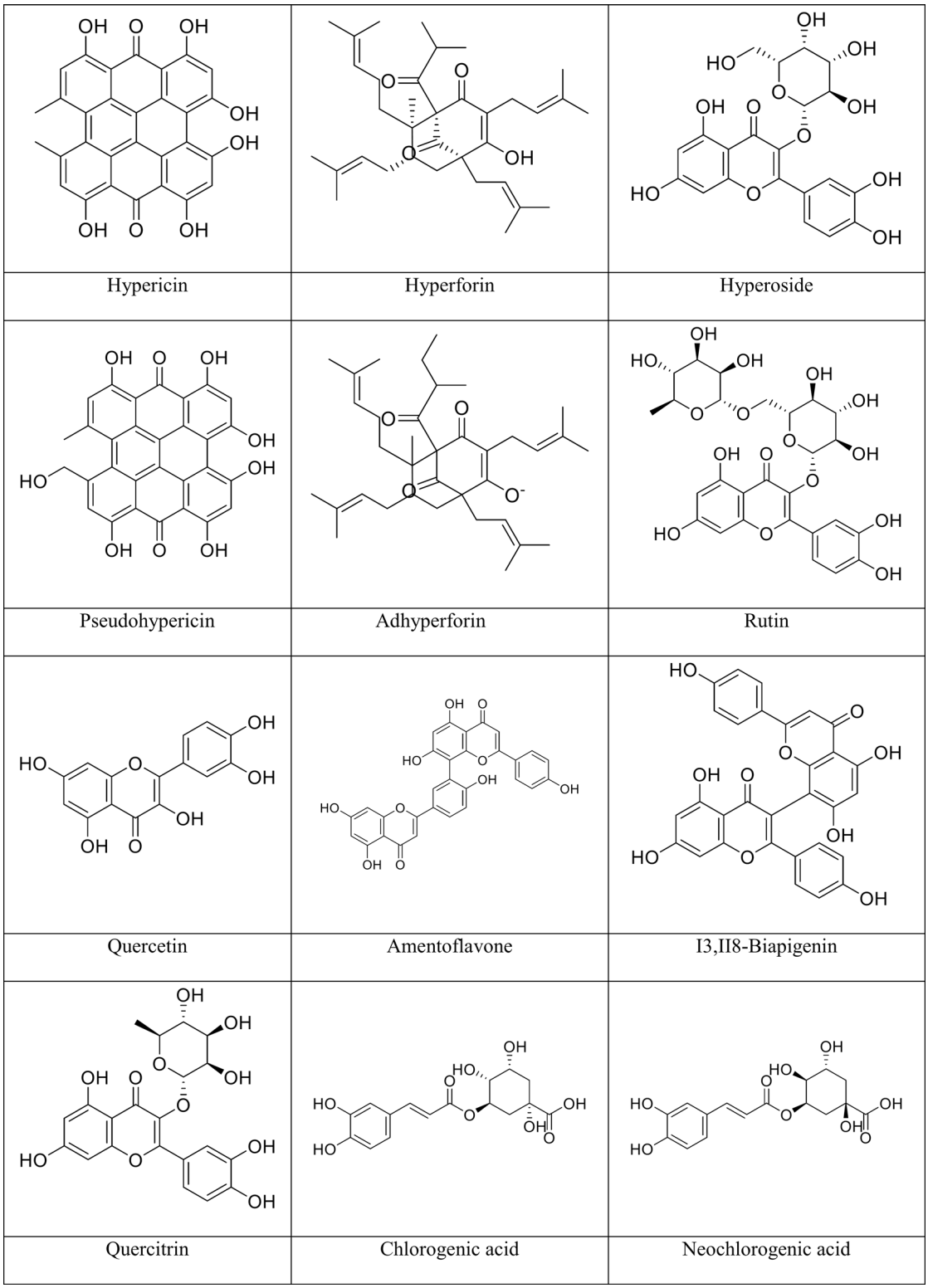

Fig. 1 Important active constituents of *Hypericum perforatum*

Table 1 *Hypericum perforatum* phytoconstituents

Phytochemical class	Corresponding phytoconstituents	References
Naphthodianthrone	Hypericin and pseudohypericin (0.03–0.3%), protohypericin, protopseudohypericin, isopseudohypericin[a], cyclopseudohypericin[b]	Naït-Si and Fourneron (2005), Saddiqe et al. (2010)
Phloroglucinol	Hyperforin (2.0–4.5%), adhyperforin/pseudohyperforin (0.2–1.9%), hyperfirin[c], adhyperfirin[d], furohyperforin[e], oxepahyperforin[f], hydroperoxycadiforin, aristoforin[g]	Gartner et al. (2005), Patočka (2003), Saddiqe et al. (2010), Tatsis et al. (2007)
Flavonoid (2–4%)	Flavonol agycones: quercetin, myricetin, luteolin, kaempferol, catechin, epicatechin	Barnes et al. (2001), Saddiqe et al. (2010), Silva et al. (2005), Tusevski et al. (2016)
	Flavonol glycosides: rutin, hyperoside/hyperin, quercitrin, isoquercitrin, astilbin, miquelianin, quercetin 6-C-glucoside, kaempferol 3-O-glucoside, kaempferol 3-rutinoside, rutin-acetyl	
Biflavone	Amentoflavone (0.01–0.05%), I3,II8-biapigenin (0.1–0.5%), I6, II8-diquercetin	Saddiqe et al. (2010)
Phenolic acid	Chlorogenic acid[h] (<1%), neochlorogenic acid[i], caffeic acid (0.1%), gentisic acid, shikimic acid, *p*-coumaric acid, 3-O-coumaroylquinic acid, ferulic acid, isoferulic acid, 3-feruloylquinic acid[j]	Saddiqe et al. (2010), Silva et al. (2005), Tusevski et al. (2016)
Proanthrocyanidin (2–4%)	Dimeric procyanidin B2 and other dimeric, trimeric, tetrameric procyanidins	Patočka (2003)
Essential oil (0.05–0.9%)	Hydrocarbons: n-octane, 2-methyloctane, nonane, 3-methylnonane, decane, 2-methyldecane, dodecane, cyclododecane, tridecane, undecane, 5-methylundecane	Barnes et al. (2001), Ghasemi Pirbalouti et al. (2014), Hosni et al. (2011)
	Monoterpenoids: *p*-cymene, limonene, β-myrcene, β-ocimene, α-phellandrene, pinene, sabinene, terpinene, terpinolene, α-thujan, carvacrol, 1,8-cineol, geraniol, pulegone	
	Sesquiterpenoids: α-amorphene, aromadendrene, bicyclosesquiphellandrene, β-bourbonene, 1,4-cadinadiene, cadinene, caryophyllene, caryophyllene oxide, α-cedrene, α-copaene, cubebene, β-elemene, farnesene, germacrene-D, β-himachalene, humulene, ledene, α-longipinene, nerolidol, selinene, spathulenol, viridiflorol, ylangene, zingiberene	
	Others: α-cadinol, phytol, α-terpineol,2-methyloctan-1-ol, dodecanol, hexanal, n-nonanal, 2-pentadecanone	
Xanthone (0.01%)	Kielcorin C, norathyriol, roeperanone, mangiferin, mangiferin C-prenyl hexoside, 1,3,6,7-tetrahydroxyxanthone, 1,3,7-trihydroxy-2-(2-hydroxy-3-methyl-3-butenyl)-xanthone, trihydroxy-1-methoxy C-prenyl xanthone, 1,5-dihydroxy-2-methoxyxanthone	Greeson et al. (2001), Saddiqe et al. (2010), Tusevski et al. (2016)
Amino acid (0.01%)	γ-Amino butyric acid (0.0007%), cysteine, glutamine, leucine, lysine, ornithine, proline, threonine	Greeson et al. (2001)
Fatty alcohol	1-Dodecanol, 1-tetracosanol, 1-hexacosanol, 1-octacosanol, 1-triacontanol	Brondz et al. (1983)

[a,b] Isopseudohypericin is isomer of pseudohypericin, formed at pH 5–10. Pseudohypericin is stable below pH 5, whereas isopseudohypericin is stable above pH 10. Cyclopseudohypericin is an oxidation product of pseudohypericin

[c,d] Hyperfirin and adhyperfirin are reported to be biosynthetic precursors of hyperforin and adhyperforin, respectively

[e,f] Furohyperforin and oxepahyperforin are hyperforin oxidation products, former being a major degradant

[g] Aristoforin is equipotent synthetic analogue of hyperforin, not occurring naturally

[h,i] Chlorogenic acid and neochlorogenic acid are same as 3-O-caffeoylquinic acid and 5-O-caffeoylquinic acid, respectively

[j] 3-Feruloylquinic acid was found exclusively in HYP callus cultures

derived from chalcone backbones formed by the phenylpropanoid pathway (Falcone Ferreyra et al. 2012).

Bioactives of HYP can be segregated based on their polarities; phloroglucinol > naphthodianthrones, xanthones, essential oils, biflavones > flavonoids > proanthrocyanidines, phenolic acids, being the decreasing order of lipophilicities. Understanding of polarities help in selection of extraction solvents and pharmaceutical vehicles (Wolfle et al. 2014). Hypericin contents of extracts are reported to remain almost constant for 50% and above concentrations of methanol or ethanol in hydroalcoholic extractants. Best yields of hyperforin and adhyperforin are obtained with 70% ethanol, while concentrations below 50% barely procure the same (Langer 2009). Direct sonication of HYP crude drug delivers remarkably high hypericin, hyperforin and flavonoid contents compared to other methods, including Soxhlet extraction method (Smelcerovic et al. 2006). Extraction of HYP by liquid CO_2 ($p = 80$ bar, t = 15 °C) or supercritical CO_2 ($p = 100$ bar, t = 40 °C) reportedly gave similar yields. Though in supercritical method, pulverized crude gave richer extract under higher pressure (250–350 bar), due to increased solubilisation of phytoconstituents (Smelcerovic et al. 2004).

Hypericin and pseudohypericin contents of wild HYP plants tend to vary with seasonal changes (Southwell and Bourke 2001). A study assessed effects of exogenous and endogenous factors on quality of HYP crude drug by maintaining controlled environmental conditions with growth chambers. Harvesting times, temperatures and reproduction conditions were varied as per the protocol, but soil pH, photoperiod, humidity, etc. were kept uniform throughout the experiment. Change in any of the three conditions showed a significant impact on production of hypericin, pseudohypericin and hyperforin. Therefore, cultivation of HYP in controlled habitat promises to deliver quality in crude drugs; by minimizing geographical, propagative and seasonal variations (Couceiro et al. 2006). A comparative study was held on cultivated HYP plants divided into healthy or ribosomial group 16SrVII phytoplasma infected types. Methanolic extracts of dried flowering tops of infected plants contained lower concentrations of rutin, hyperoside, isoquercitrin, amentoflavone and pseudohypericin, but higher concentrations of chlorogenic acid and sesquiterpenes than the similar extracts of healthy plants. Hypericin, quercitrin and quercetin contents remained almost unaffected, whereas essential oil and hydrocarbon contents were drastically reduced in infected plants. Hence, phytopathological conditions possess potential to alter the commercial and therapeutic quality of cultivated HYP plants (Bruni et al. 2005). However, optimized plant tissue culture techniques have enabled faster and higher production of selective phytoconstituents of HYP in adventitious root and callus cultures (Tusevski et al. 2016; Walker et al. 2002; Wu et al. 2014).

Pharmacological activities

Enormous scientific data generated from preclinical and clinical studies support the medicinal use of HYP. Biological activities depicted by standardized *H. perforatum* extracts (HYPEs) are summarized in Table 2.

Antidepressant activity

Synthetic antidepressants increase synaptic concentration of one or more neurotransmitters by blocking their reuptake or metabolic degradation and exert the desired effects (Brunello et al. 1994). Though the standardized HYPEs display antidepressant activity parallel to synthetic contenders, their mechanism of action is still unclear (Wang et al. 2010). Postulations put forth by researchers help to shed light on this anonymity.

Preclinical studies performed with *H. perforatum* extract (HYPE) LI-160 proposed non-selective monoamine oxidase inhibition and neurotransmitter reuptake inhibition to be the underlying mechanisms of its antidepressant effect. Additionally, along with down-regulation of beta-adrenoceptors, it was reported to cause up-regulation of cortical serotonergic-receptors (Muller et al. 1997); which contradicted the usual outcome of antidepressants (Celada et al. 2004). *In vivo* studies conducted with acute doses (50 and 200 mg/kg, p.o.) of standardized HYPE showed increased dopamine and noradrenaline concentrations but decreased serotonin concentrations in several rat brain regions (Kumar et al. 2001). Since no pinpoint conclusion could be drawn from these findings; investigation of action mechanism continued and led

Table 2 Pharmacological activities of *Hypericum perforatum*

Activity	Active phytoconstituent[a]	Reported mechanism of action	References
Antidepressant activity	Hypericin	Non-selective monoamine oxidase inhibition and/or competitive antagonism at CRF receptors and/or augmentation of presynaptic action potential duration by delayed rectifier potassium currents	Butterweck et al. (2004), Jensen et al. (2001), Leuner et al. (2007), Simmen et al. (2003), Suzuki et al. (1984), Thiede and Walper (1994), Tian et al. (2014), Wang et al. (2010)
	Pseudohypericin	HPAA hyperactivity control by selective antagonism at CRF receptors	
	Hyperforin	Non-competitive antagonism at CRF receptors and/or non-selective neurotransmitter reuptake inhibition by TRPPC-6 mediated membrane sodium gradient breakdown	
	Adhyperforin	Non-selective neurotransmitter reuptake inhibition by binding to serotonin and noradrenaline transporters	
	Flavonoids	Delayed expression of genes controlling HPAA hyperactivity and/or Catechol-O-methyl transferase inhibition	
	Xanthones	Catechol-O-methyl transferase inhibition	
Antiparkinsonian activity	Hyperforin and quercetin	Monoamine oxidase-B inhibition and/or reduction in DNA fragmentation, astrogliosis, oxidative stress and inflammation	Gomez del Rio et al. (2013), Kiasalari et al. (2016), Mohanasundari and Sabesan (2007)
Anticonvulsant activity	Aqueous fraction of ethanolic HYPE	Nitric oxide synthase mediated pathway	Hosseinzadeh et al. (2005), Ivetic et al. (2002)
Antidementia activity	Hyperforin	Potentiation of cognitive behaviour and/or control of elevated brain oxidative stress, induction of P-gp which transports beta-amyloid from the brain into the blood	Brenn et al. (2013), El-Sherbiny et al. (2003), Klusa et al. (2001)
Antioxidant activity	Hyperforin and aristoforin[b]	Free radical scavenging properties	Meinke et al. (2012), Orcic et al. (2011), Sevcovicova et al. (2015), Zou et al. (2004)
	Flavonoids	Metal-chelation, free radical scavenging and reactive oxygen quenching properties	
	Phenolic acids	Unknown	
Antimicrobial activity	Antimalarial activity: Hyperforin	Active against *Plasmodium falciparum*	Avato et al. (2004), Barnes et al. (2001), Verotta et al. (2007)
	Antiviral activity: Hypericin, pseudohypericin, flavonoids, catechin	Unknown	
	Antibacterial and antifungal activity: Hyperforin[c], hypericin	Primarily active against gram-positive bacteria	
Wound healing activity	Synergistic effect of hypericin, hyperoside, isoquercitrin, rutin and epicatechin	Integrated antimicrobial, antioxidant and anti-inflammatory activities	Süntar et al. (2010), Wolfle et al. (2014)

Table 2 continued

Activity	Active phytoconstituent[a]	Reported mechanism of action	References
Anti-inflammatory activity	Hypericin	Antihyperalgesic effect by inhibition of neuropathic stimuli-induced over-expression of protein kinase C and their phosphorylation	Abdel-Salam (2005), Galeotti et al. (2010), Hammer et al. (2007), Huang et al. (2011), Sosa et al. (2007), Zdunić et al. (2009)
	Hyperforin	Antihyperalgesic effect by opioid-dependent pathway and/or prostaglandin E2 inhibition	
	Pseudohypricin, amentoflavone, I3, II8-biapigenin, quercetin, chlorogenic acid, adhyperforin	Prostaglandin E2 inhibition	
Antiangiogenic activity	Hyperforin, octahydrohyperforin[b]	Inhibition of tumour triggered angiogenesis	Lorusso et al. (2009), Martinez-Poveda et al. (2010)
Anticancer activity	Hypericin	Photosensitizer, which produces necrosis-inducing reactive oxygen moieties on irradiation with visible light of suitable wavelength. Also, tumour visualization probe, which imparts fluorescence selectively to tumour cells	Maduray and Davids (2011), Ritz et al. (2012b), Šemeláková et al. (2012)
	Hyperforin and aristoforin[b]	Unknown	

[a] Identification of anxiolytic, anti-addiction, antiobesity, antidiabetic and hepatoprotective phytoconstituents of HYP is not reported yet (Arokiyaraj et al. 2011; Bayramoglu et al. 2014; Catania et al. 2003; Kumar and Singh 2007; Perfumi et al. 2005b; Richard et al. 2012)

[b] Equipotent or stronger synthetic analogues of hyperforin

[c] Imanin is a hyperforin rich antibacterial mixture extracted from HYP using water-alkali solution (Nikolic and Zlatkovic 2010)

to new hypotheses. *In vivo* microdialysis studies performed on awake rats for a single dose of HYPE (60 mg/kg, i.p. or 300 mg/kg, p.o.) reported significant increase in dopamine levels, but only a moderate augmentation of serotonin levels. Besides, noradrenaline levels remained unaffected for both the dose administration routes. This proclaimed mechanism of action of HYP to be more complex than that of synthetic analogues; probably involving a reduction in the depression associated anhedonia through elevated dopamine levels or so (Yoshitake et al. 2004). In a study carried out on male rats with 1 mg/kg, p.o. dose, HYPE set off maximum dopamine release in nucleus accumbens and striatum after 100 and 80 min post administration lag time, respectively (Di Matteo et al. 2000). Experimenting on rats kept under chronic restraint stress for 21 consecutive days demonstrated that standardized extract STW3-VI (125–750 mg/kg, p.o.) could raise thymus and spleen indices and lower stress-induced markers such as plasma levels of adrenocorticotropic hormone and corticosterone. Hence, therapeutic effect of HYP was suggested to be integrated through immune, oxidative defence and neuroendocrine systems (Grundmann et al. 2010). Neuroendocrine investigations undertaken in past have also hinted at the involvement of HYP in regulation of genes that control hypothalamic–pituitary–adrenal axis (HPAA) function (Butterweck et al. 2003a). Hyperactivity of HPAA is sometimes indicative of depression (Vreeburg et al. 2009). Although in vitro results of a study correlated antidepressant effect of HYP with metabolite or endogenous ligand mediated sigma receptor activation, in vivo demonstration of the same was doubtful (Mennini and Gobbi 2004).

To identify the exact phytoconstituents ascribing antidepressant activity to HYP, researchers looked into the details of its isolated important actives. In an analysis conducted with three different hydroalcoholic HYPEs, antidepressant effect was evaluated from tail

suspension test in mice and forced swimming test in rats. Two extracts contained hypericin (0.14%) and flavonoids (12%), one each and remaining contained hypericin (0.15%) as well as hyperforin (3.2%). From the observations, contribution of all the three phytoconstituents in antidepressant activity of HYP was inferred (Butterweck et al. 2003b). Increased corticotropin-releasing factor (CRF) levels play an important role in hyperactivity of HPAA. Hypericin, pseudohypericin and hyperforin caused CRF receptor antagonism in recombinant Chinese hamster ovary cells, proving their antidepressant effect. However, only pseudohypericin demonstrated selective antagonism against CRF receptors. The CRF stimulated cAMP formation was used as marker for these studies (Simmen et al. 2003). Comparative clinical trials with standardized HYPEs WS 5573 (0.5% hyperforin) and WS 5572 (5% hyperforin) concluded that optimum hyperforin content is necessary for antidepressant activity of HYPE (Laakmann et al. 1998). Since, adhyperforin showed neurotransmitter reuptake inhibition along with binding affinities for serotonin and noradrenaline transporters, its antidepressant action is evident (Jensen et al. 2001; Tian et al. 2014).

Although earlier findings associated flavonols and xanthones with catechol-O-methyl transferase inhibition and hypericin with monoamine oxidase inhibition (Suzuki et al. 1984; Thiede and Walper 1994), expanding boundaries of research gave newer possibilities. Studies conducted on primary cultures of neonatal rat hippocampal neurones suggested that hypericin augments presynaptic action potential duration by delaying rectifier potassium currents and reduces synaptic neurotransmitter deficiency (Wang et al. 2010). In recent studies, treating pregnant Wistrar rats during gestation period with 72 or 144 mg/kg daily oral doses of aqueous HYPE subsided symptoms of postpartum depression up to 60 subsequent days. The extract in dry form contained 0.3% hypericin and lowered depression without any side effects (Vieira et al. 2013). In an analysis performed on rat test models exposed to chronic unpredictable mild stress, hypericin displayed better curative activity than a marketed synthetic antidepressant Venlafaxine (Zhai et al. 2015). In contrast to hypericin and flavonoids, hyperforin does not have delayed effect on expression of genes that control hyperactivity of HPAA in mood disorders (Butterweck et al. 2004; Butterweck et al. 2003a). Nevertheless, hyperforin displayed non-selective neurotransmitter reuptake inhibition (IC_{50} = 0.05–0.10 μg/ml) (Chatterjee et al. 1998) and down-regulation of cortical beta-adrenoceptors in rats treated subchronically with hyperforin enriched extracts (Muller et al. 1998). The dopamine transporter binding site of hyperforin differed from that of synthetic reuptake inhibitors, suggesting unlike site of coherence or altogether different mechanism of action (Jensen et al. 2001). The serotonin reuptake inhibition was reported to occur due to the increase in intracellular free sodium ions (Singer et al. 1999) through activation of non-selective cation channels. Inhibition of hyperforin by lanthanide (La^{3+}) and gadolinium (Gd^{3+}) ions suggested homology between non-selective cation channel and transient receptor potential protein channel (TRPPC) (Treiber et al. 2005). Further studies identified TRPPC-6 to be hyperforin binding target and postulated that hyperforin activates TRPPC-6 and elevates intracellular sodium ion concentration. This causes breakdown of membrane sodium gradient, which in turn inhibits neurotransmitter reuptake (Leuner et al. 2007). Analysis of hyperforin treated (4 mg/kg/day, i.p. for 4 weeks) adult mice brain proposed brain cortex to be an important hyperforin-target; since, expression of cortical brain-derived neurotrophic factor receptor had augmented, but hippocampal neurogenesis was unaffected (Gibon et al. 2013).

Although the uncertainty of mechanism persists, the efficacy of standardized HYPEs in management of depression is manifested by clinical trials. Controlled trials proved HYPE to be an herbal antidepressant drug with very few incidents of side effects (Nordfors and Hartvig 1997). For a long term clinical study conducted with HYPE WS 5570, data reanalysis was done for the subset of patients suffering from an acute episode of mild depression. At the end of 6 week treatment, 25% patients in placebo group, 57% patients in 600 mg/day dose group, 33% patients in 900 mg/day dose group and 62% patients in 1200 mg/day dose group showed relief from symptoms. Hence, in acute treatment of mild depression, extract WS 5570 displayed efficacy coupled with likelihood of suspension of the ailment (Kasper et al. 2008). A randomized, double-blind, multicentre clinical trial was conducted for 8 weeks using HYPE STEI 300 at dosing frequency of 350 mg/thrice a day. Measurements on Hamilton depression scale established it to be equally effective in moderate depression as imipramine (100 mg/day dose), with side effects as low as placebo (Philipp et al. 1999). In

placebo-controlled clinical trials, HYPE WS 5570 (600–1200 mg/day for 6 weeks) (Kasper et al. 2006; Lecrubier et al. 2002) and WS 5572 (900 mg/day for 42 days) (Kalb et al. 2001) were found more effective than placebo in mild to moderate depression patients. In an open-label trial, 440 outpatients of mild to moderate depression were treated with 500 mg/day dose of HYPE ZE 117 for a year. Treatment success with less than 10% treatment related adverse effects indicated its use to be safe in prevention of condition relapse (Brattstrom 2009). Treating moderate depression with HYPE STW 3-VI also showed reduced relapse events and improved relief duration (Singer et al. 2011). Results of a randomized, double-blind trial conducted for 12 weeks indicated HYPE LI-160 (900 mg/day) to be remarkably more effective than fluoxetine (20 mg/day) in mitigation of major depression (Fava et al. 2005). In contrast, another double-blind, randomized, placebo-controlled trial reported activity of standardized HYPE LI-160 to be no better than the placebo in moderately severe major depression (Hypericum Depression Trial Study Group 2002). Authors deduced the same conclusion even after reanalysis of this trial assuming missing data process (Grobler et al. 2014). In a randomized, double-blind, placebo-controlled clinical trial involving 200 outpatients with major depression, all participants were kept on single-blind placebo run for a week, followed by changing randomly to either standardized HYPE ($n = 98$; 900 mg/day for 4 weeks, shifting to 1200 mg/day if inadequate response) or placebo ($n = 102$) for 8 weeks. From the Hamilton depression scale scoreboard, HYPE failed to restore the mental health of major depression patients (Shelton et al. 2001).

In a nutshell, standardized HYPE is an economical alternative to generic antidepressants in treatment of mild to moderate depression. But, its therapeutic ambiguity in major depression holds a scope for further investigation and clarity on the same (Solomon et al. 2013).

Antiparkinsonian activity

Various preclinical trials have investigated the effectiveness of HYP in Parkinson's disease; however, information on clinical trials is not available. In an in vivo study, 7 day treatment with methanolic HYPE (300 mg/kg/day, p.o.) demonstrated protective effect against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity in mice (Mohanasundari et al. 2006a). Extension of these studies suggested synergistic effect of methanolic HYPE (300 mg/kg/day, p.o.) and bromocriptine (10 mg/kg/day, i.p.) to be markedly high than the effect of either alone (Mohanasundari et al. 2006b). Also, significant monoamine oxidase-B inhibition and reduced astrocytes activation was achieved in mice brain striatum, which indicated a decrease in dopaminergic neurodegeneration (Mohanasundari and Sabesan 2007). In another study, intrastriatal 6-hydroxydopamine lesioned rats were treated with hydroalcoholic HYPE (200 mg/kg/day) for 2 weeks, 1 before and 1 after the surgery. The results correlated reduction in parkinsonism to HYP-induced reduction in DNA fragmentation, astrogliosis, oxidative stress and inflammation (Kiasalari et al. 2016). Comparative studies on rotenone-induced neurodegeneration rat models, between quercetin liposomes and two standardized HYPEs containing 6% and 0.2% hyperforin, suggested hyperforin and quercetin are vital in neuroprotection (Gomez del Rio et al. 2013).

Anticonvulsant activity

Antiepileptic properties of HYP, not very long known, are only scarcely researched so far. In experiments performed on mice under picrotoxin-induced seizures, 50 mg/kg, i.p. dose of methanolic HYPE displayed better effect than 100–200 mg/kg, i.p. doses. This merely confirmed the presence of anticonvulsant properties in HYP (Etemad et al. 2011). In a study conducted with 1 ml/kg, i.m. single dose at-a-time, either of water, n-butanol or ether fractions of ethanolic HYPE, the bioelectric activity was registered with electrodes chronically implanted in cortical and hippocampal regions of Chinchilla rabbits. The effects of kindling epilepsy were observed to be in correlation with polarity of phytoconstituents. The water fraction demonstrated highest antiepileptic activity, whereas ether one benefited the epileptic effects (Ivetic et al. 2002). Researchers further extended these studies to investigate effect of HYPEs on epileptogenesis; where water and n-butanol extracts reduced the hyper-synchronous neuronal firing alongside shortening its duration (Ivetic et al. 2011). Anticonvulsant activities of aqueous and ethanolic HYPEs were examined in mice using pentylenetetrazole and maximal electroshock seizure tests. The individual doses (0.1 or 1 g/kg, i.p.) of both

the extracts delayed onset of tonic convulsions in former test but proved absolutely ineffective in latter test. Furthermore, administration of nitric oxide synthase inhibitor reduced the antiepileptic effect. Hence, authors hypothesised partial involvement of nitric oxide pathway in anticonvulsant mechanism of HYP and recommended its use to control petit mal seizures (Hosseinzadeh et al. 2005). Though anticonvulsant activity of HYP is proved, its contributor, mechanism and clinical efficacy are yet to be unveiled.

Antidementia activity

In a conditioned avoidance test, hyperforin (1.25 mg/kg/day) or HYPE (50 mg/kg/day) were orally administered to rat for a week. The test outcome showed that the responses acquired through training were retained even on 9th day following discontinuation of treatment and training. In passive avoidance response test performed on mouse, a single oral dose (1.25 mg/kg) of hyperforin enhanced memory acquisition and reversed scopolamine-induced amnesia to a considerable extent, whereas single HYPE dose (25 mg/kg) was ineffective. Hence, hyperforin was reported to potentiate cognitive behaviour and impart antidementia activity to HYPE (Klusa et al. 2001). Low doses of HYPE were said to exert antioxidant activity against elevated brain oxidative stress in amnesia. Since, depression frequently associates with dementia; HYP is suggested to be suitable remedial candidate possessing binary effectiveness (El-Sherbiny et al. 2003). P-glycoprotein is known to transport beta-amyloid from the brain into the blood. The HYPE (5% hyperforin) demonstrated decreased beta-amyloid accumulation and increased P-gp expression in mice brains. Hence, HYP appears to control progression of Alzheimer's disease through P-gp induction (Brenn et al. 2013). But, since HYPE showed anti-dementia activity in mice even in absence of hyperforin, the active constituent remains unclear (Hofrichter et al. 2013).

Anxiolytic activity

In a test assessing anxiolytic activity of HYP in mice, treatment with HYP (200 and 400 mg/kg, p.o.) alone or with imipramine (10 mg/kg, i.p.) proved efficacious against 72 h sleep deprivation- induced anxiety (Kumar and Singh 2007). Anxiolytic effect of HYP was also seen in mice displaying anxious behaviour induced by 6 h acute restraint stress (Prakash et al. 2010) or chronic corticosterone treatment (Crupi et al. 2011).

Antiaddiction activity

Very few attempts have investigated the potential of HYP in alcoholism and nicotinism reversal. The CO_2 extract of HYP alone (125 mg/kg, i.p.) or with co-administered naltrexone (0.5 mg/kg, i.p.) showed reduction in ethanol intake of Marchigian Sardinian alcohol-preferring rats. Also, the 12 day chronic treatment didn't develop tolerance (Perfumi et al. 2005a). Further investigation demonstrated reduced ethanol self-administration in rats treated with 31 or 125 mg/kg, i.p. doses of CO_2 extract of HYP (Perfumi et al. 2005b). In a study evaluating HYP activity in ethanol withdrawal syndrome, adult male Wistar rats were subjected to liquid diet (ethanol 7.2% v/v) for 15 days. After discontinuation of diet, locomotor hyperactivity, stereotyped behavior and tremors were monitored for 6 h as withdrawal symptoms. *H. perforatum* extract controlled withdrawal symptoms in a dose-dependent manner (Coskun et al. 2006). Since, HYP also reduced nicotine withdrawal symptoms in mice, its use is suggested for smoking cessation (Catania et al. 2003).

Antioxidant activity

In a study evaluating antioxidant activity of HYP, standardized HYPE demonstrated inhibition of H_2O_2-induced oxidative damage on pheochromocytoma cell line. Furthermore, Fe^{2+}/ascorbate induced lipid peroxidation of rat brain cortex mitochondria was inhibited too (Benedí et al. 2004). Another study testing standardized HYPE (4 mg/kg, i.p.) on rotenone treated rat brain homogenates suggested its use in the treatment of elderly patients experiencing oxidative stress induced neurodegeneration (Sánchez-Reus et al. 2007). Acetonic HYPE was reported to contain highest amounts of flavonoids and phenolic acids but, showed least antioxidant effect (IC_{50} = 105.9 µg/ml); whereas, the ethanolic extract (IC_{50} = 7.8 µg/ml) showed better potency than butylated hydroxytoluene (IC_{50} = 12.77 µg/ml) (Maskovic et al. 2011). In a comparative study, HYP exerted better antioxidant effect than synthetic antioxidants. Analysis of

ethanolic HYPE attributed antioxidant activity of HYP to flavonoids and phenolic acids, while hypericin and hyperforin were claimed to barely possess the same (Orcic et al. 2011; Silva et al. 2005). However, free radical scavenging properties of hyperforin were shown later through preclinical as well as clinical trials. The in vitro evaluation included irradiation of keratinocytes with solar simulated radiation, whereas ex vivo evaluation included irradiation of hyperforin-rich cream applied porcine ear skin with infrared radiation. Hyperforin demonstrated a high radical scavenging effect in both the studies. Moreover, in randomized, double-blind, vehicle-controlled, clinical trial, the ultraviolet radiation-induced erythema was significantly reduced by hyperforin cream (Meinke et al. 2012). The free radical scavenging activity imparts DNA protective effect to hyperforin, and is also retained by its synthetic analogue aristoforin (Sevcovicova et al. 2015). Antioxidant mechanism of flavonoids include metal-chelation, free radical scavenging and reactive oxygen quenching effects (Zou et al. 2004). Failure to prevent oxidative damage to proteins and stimulation of pro-oxidant protein damage by HYPE is also reported (Gioti et al. 2009).

Antimalarial activity

Hyperforin is reported to be active against *Plasmodium falciparum* with IC_{50} value in a micromolar range. It was found orally active and more potent than other HYP phloroglucinols (Verotta et al. 2007).

Antiviral activity

Antiviral activity of HYP is one of its early identified biological activities. A former review had reported influenza virus inhibition by flavonoid and catechin containing fractions of HYPE. Hypericin and pseudohypericin too have shown in vitro activity against human immunodeficiency virus and type 1 and 2 herpes simplex viruses. Besides these, hypericin has also inactivated murine cytomegalovirus, Sindbis virus and hepatitis C virus (Barnes et al. 2001). A study conducted phase I clinical trial to assess safety and antiviral activity of hypericin in chronic hepatitis C patients. Twelve patients received 0.05 mg/kg and 7 patients received 0.10 mg/kg daily oral dose of hypericin for 8 weeks. Treatment concluded absolute absence of antiviral activity against hepatitis C virus (Jacobson et al. 2001). Such inconsistent findings were said to arise from inaccurate design parameters resulting from lack of clarity on virucidal mechanisms of hypericin (Kubin et al. 2005).

Antibacterial and antifungal activity

Initially, inhibitory activity of hyperforin was evident against gram-positive bacteria, however not against gram-negative bacteria (Barnes et al. 2001). But, the forthcoming research gave newer outcomes. In an antibacterial study carried out with methanol, ethanol, petroleum ether and chloroform HYPEs, highest activity was displayed by the ethanolic extract. The chromatographic separation of ethanolic extract demonstrated presence of hypericin, hyperforin and flavonoids. On incubation of gram-positive microbes with individual components, hypericin and hyperforin showed considerable bactericidal activity, but flavonoids displayed complete inactivity (Avato et al. 2004). For similar ethanolic extract, another study reported sensitivity of gram-negative types as well, with minimum inhibitory concentration range of 1.25–3.5 mg/ml. The extract also demonstrated peak fungistatic properties at 45 mg/ml concentration (Milosevic et al. 2007). A study reported antifungal activity of ethanolic and ethereal HPYE with minimum inhibitory concentration of 20 mg/ml, but flavonoids and phenolic acid rich acetonic extract was inactive (Maskovic et al. 2011). Methanol-acetone HYPE also exhibited activity against gram-positive and gram-negative bacteria. Besides, contribution of constituents other than hypericin and hyperforin was suggested, but fell short of confirmation (Cecchini et al. 2007).

Imanin is an antibacterial mixture obtained from extraction of HYP using water-alkali solution as an extractant. A study examined antibiotic potential of imanin against a range of gram-positive bacteria using disc diffusion method. Imanin was prepared from wild HYP samples collected at various growth intervals viz., spring sprouts, budding, initial bloom, full blossoming, fructification beginning, pod ripening and haulm withering. On chromatographic separation, imanin showed presence of hypericin, pseudohypericin, hyperforin, hyperoside, isoquercitrin, quercitrin, quercetin and catechin; hyperforin being the principal constituent. Though antibiotic activity of imanin existed for whole range of gram-positive bacteria, its

potency varied with sample collection intervals. Hence, the study correlated highest activity of imanin with highest hyperforin content i.e. at the budding or full blossoming intervals of the plant (Nikolic and Zlatkovic 2010). Similarly, variation in geographical sources impacted antibacterial and antifungal properties of HYPEs (Conforti et al. 2005).

Wound healing activity

An antimicrobial activity of HYP partly provides the rationale behind its traditional use as a salve (Saddiqe et al. 2010). Pragmatic details obtained from systematic research further justify its application as a wound healer. A study testing wound healing activity of HYPE on cultured chicken embryonic fibroblasts analysed mitotic ability, morphologic changes and collagen production in stained cells as the markers of lesion repair. On incubation with HYPE, fibroblasts assumed polygonal shape and displayed increased collagen levels, which indicated wound healing (Ozturk et al. 2007). Yet, due to the discrepancies in fibroblast migration and collagen synthesis stimulation, wound healing profiles varied amongst HYP subspecies (Dikmen et al. 2011). In an investigation, ethanolic extract of aerial parts of HYP demonstrated excellent healing properties in excision as well as incision wound models. The contents of ethanolic extract were then partitioned using ethyl acetate, and ethyl acetate fraction was examined on same experimental models. The results attributed wound healing activity to synergistic effects of hypericin, hyperoside, isoquercitrin, rutin and epicatechin (Süntar et al. 2010).

A formulation containing olive oil HYPE and essential oils of sage and oregano demonstrated in vivo wound healing activity in rats and mice. Histopathological studies evinced that ointment of HYP alone was active too, but less effective in comparison to the formulation (Suntar et al. 2011). *In vivo* surgical skin incision healing induced by HYP dermal gel and microcurrent (10 μA/2 min) was found to be significantly high than that by HYP dermal gel alone (Castro et al. 2012). In a clinical study undertaken to evaluate the efficacy of HYP and *Calendula arvensis* lipid extract combination, the mixture palliated caesarean gash and accelerated recovery (Lavagna et al. 2001). Nine patients in the age group of 63–90 years were engaged in clinical trial assessing efficacy of wound dressing on post-surgical scalp wounds with exposed bone. The wound dressing was a phytopharmaceutical prepared from combination of HYP and *Azadirachta indica* oils. After treatment of 4 weeks, tissue was restored on entire exposed bone surface in 67% patients, whereas mean exposed bone area was reduced in 95% patients (Lauchli et al. 2012). Hence, it is evident that appropriate amalgamations enhance the inherent wound healing effect of HYP and potentiate its dermatological applications (Wolfle et al. 2014).

Anti-inflammatory activity

Salving effect of HYP is contributed by its anti-inflammatory properties also (Süntar et al. 2010). In an inflammatory bowel disease trial, ulcerative colitis was induced in 70 rats by loading 2 ml of 3% acetic acid into colon of each rat. Treatment outcomes for oral HYPE (1 ml/day of 600 and 300 mg/kg) and intra-colonic gel (1 ml/day of 20% and 10%) were evaluated by monitoring histopathological changes and tissue malondialdehyde levels after 7 days. Both the dosage forms were found to alleviate inflammation in dose dependent manner, higher doses being more effective (Tanideh et al. 2014). Therapeutic effect of HYPE was also seen in rats with 2,4,6-trinitrobenzene sulfonic acid-induced inflammatory bowel disease (Dost et al. 2009). Antiedematogenic and antihyperalgesic properties of HYP are reported to help in inflammatory pain management (Abdel-Salam 2005). The antihyperalgesic effect of HYP was studied in two rat models against neuropathic pain induced through chronic constriction injury and repeated administration of oxaliplatin. At 30–60 mg/kg, p.o. doses of HYP, mechanical hyperalgesia was reversed up to next 180 min. Hyperforin and hypericin were found to be the antihyperalgesic actives. Hypericin subsides neuropathic stimuli-induced over-expression of protein kinase C and their phosphorylation, whereas hyperforin acts via opioid-dependent pathway (Galeotti et al. 2010). Apart from these, pseudohypricin, amentoflavone, I3,II8-biapigenin, quercetin, chlorogenic acid and adhyperforin were reported to exhibit good anti-inflammatory activity (Huang et al. 2011; Sosa et al. 2007; Zdunić et al. 2009). The pseudohypericin, hyperforin and flavonoids response is said to be exerted through prostaglandin E2 inhibition (Hammer et al. 2007). Overall anti-inflammatory effect of

HYP is suggested to result from synergistic interactions of its actives, though the mechanisms remain unknown (Hammer and Birt 2014).

Antiangiogenic activity

Hyperforin abates neutrophil and monocyte chemotaxis in vitro and chemokine-induced angiogenesis in vivo, demonstrating potential to prevent inflammation and tumour triggered angiogenesis (Lorusso et al. 2009). Assays performed with bovine aortic endothelial cells or chorioallantoic membrane have depicted hyperforin's role in angiogenesis inhibition, leading to metastasis prevention and cancer cell apoptosis (Martinez-Poveda et al. 2005). Out of several oxidatively-altered derivatives of hyperforin, octahydrohyperforin showed a little higher potency than hyperforin itself (Martinez-Poveda et al. 2010).

Anticancer activity

Hypericin was recently found to be an herbal photomedicine capable of assisting in photodynamic therapy employed for cancer treatment. Irradiation with visible light of suitable wavelength excites the photosensitizer hypericin, which then reacts with oxygen to produce necrosis-inducing reactive oxygen moieties. Slow uptake and rapid clearance from healthy tissues impart high tumour selectivity to hypericin (Maduray and Davids 2011). Photosensitization of hypericin mainly targets mitochondria or endoplasmic reticulum-Golgi complex and induces apoptosis or macroautophagy (Theodossiou et al. 2009). Photo-activated hypericin-induced cell death was seen to occur in melanoma cell lines. Externalization of phosphatidylserines, cell shrinkage, loss of cell membrane integrity and caspase dependent as well as independent apoptotic modes were the action mechanisms (Kleemann et al. 2014). Despite in vitro and in vivo demonstration of antineoplastic properties, poor aqueous solubility and stability restrain application of hyperforin as a clinical anticancer drug. Aristoforin, a synthetic derivative of hyperforin, offers improved aqueous stability and solubility with better anticancer activity than the parent compound (Gartner et al. 2005; Gey et al. 2007). In a photodynamic therapy, sub-optimal doses of hypericin were combined with low concentrations of hyperforin or aristoforin. Although sensitivity of colon adenocarcinoma-derived cell lines HT-29 and HCT-116 differed towards the combined therapy, overall effect on cell-division inhibition and cell-death stimulation was analogous (Šemeláková et al. 2012). Efficacy of topical HYPE in photodynamic therapy was investigated in 34 patients, 8 with actinic keratosis, 21 with basal cell carcinoma and 5 with morbus Bowen. The HYPE was applied on occluded skin lesions, 2 h before irradiation with 75 J/cm^2 of red light. The treatment was continued on weekly basis for almost 6 weeks. Although the results delivered were not very pleasant, observed success asks for further research on this relatively inexpensive therapy (Kacerovská et al. 2008). In another clinical trial, water soluble formulation of hypericin (0.1 mg/kg, i.v.) demonstrated specificity and selectivity of 90% or more towards malignancies. Furthermore, it imparted them red colour due to its fluorescence, while the healthy glial tissues continued to appear blue under fluorescent filter (Ritz et al. 2012a). Hypericin also enhanced fluorescence of in vitro medulloblastomas fivefold above the autofluorescence; hence, could be used in intraoperative visualization and photodynamic treatment of malignancies (Ritz et al. 2012b).

Antiobesity activity

A study examined hypocholesterolemic effects of flavonoid rich HYPE in rats fed with cholesterol-rich diet for 16 weeks. The tested extract lowered serum total cholesterol, total triglycerides and low density lipoprotein cholesterol in cholesterol-rich diet induced hypercholesterolemia. It also slowed the lipid peroxidation process and enhanced antioxidant enzyme activity (Zou et al. 2005). Treatment of ovariectomized rats with 70% ethanolic HYPE prevented ovariectomy-induced obesity due to the estrogen-like effects of HYP against adiposity and insulin resistance (You et al. 2014). In another study testing hypolipidemic and antiobesity activities of HYP, 100 and 200 mg/kg, p.o. doses of HYP suspension were administered to normal-diet rats, high-fat-diet induced obese rats and fructose-fed rats for 15 days. Lowering of total and low-density cholesterol, inhibition of weight gain and normalization of dyslipidemia paired with improved insulin sensitivity were the treatment outcomes observed in normal, high-fat-fed and fructose-fed rats, respectively (Husain et al. 2011). In an investigation carried out with 425 botanical extracts,

HYPE inhibited insulin-induced glucose uptake in adipocytes 3T3-L1 and arrested adipogenesis (Amini et al. 2009). In continuation to these findings, HYPE exerted similar effects on human adipocytes also. However, hypericin and hyperforin isolated from HYPE lacked in same suggesting active role of other phytoconstituents. Hence, use of HYP was proposed in controlling obesity-related metabolic disorders such as diabetes mellitus (Richard et al. 2012).

Antidiabetic activity

Preclinical studies were conducted to check effect of rutin in Wistar rats experiencing streptozotocin-induced diabetes mellitus. Oral administration of rutin to diabetic rats for 45 days signified remarkable decrease in fasting plasma glucose and glycosylated haemoglobin levels, but increase in insulin, C-peptide, haemoglobin and protein levels (Kamalakkannan and Prince 2006). Diabetic rats treated for 15 days with ethyl acetate HYPE at 50, 100 and 200 mg/kg, p.o. doses showed significant dose dependant fall in fasting blood glucose levels compared to untreated rats. Hence, the antihyperglycemic activity of HYP was demonstrated (Arokiyaraj et al. 2011). Moreover, HYP is reported to curb the hyperalgesia associated with diabetes in rodents (Can et al. 2011).

Hepatoprotective activity

An in vivo study tested the effect of HYP on hepatic ischemia–reperfusion (I/R) injury in rats. Treatment with 50 mg/kg, i.p. dose, 15 min prior to ischemia,

Table 3 Herb–drug interactions of *Hypericum perforatum* (Borrelli and Izzo 2009; Henderson et al. 2002; Mannel 2004; Russo et al. 2014)

Therapeutic categories and herb–drug interaction substrates therein	Probable mechanism	Clinical impact
Antineoplastic (docetaxel, imatinib, irinotecan); Hypolipidemic (atorvastatin, simvastatin); Immunosuppressant (cyclosporine, tacrolimus)	Induction of CYP3A4 and/or P-gp	Decreased drug bioavailability
Anticonvulsant (carbamazepine, phenobarbitone, phenytoin); Antimicrobial (erythromycin); Antiviral (efavirenz, indinavir, nelfinavir, nevirapine, ritonavir, saquinavir); Cardiovascular (verapamil); Corticosteroid (budesonide, dexamethasone, prednisone, prednisolone)	Induction of CYP3A4	Decreased drug bioavailability
Antiallergic (fexofenadine); Cardiovascular (digoxin, talinolol); Non-steroidal anti-inflammatory (ibuprofen)	Induction of P-gp	Decreased drug bioavailability
Oral contraceptive (desogestrel, ethinylestradiol, norethindrone)	Induction of CYP3A4 and/or CYP1A2	Intermenstrual bleeding
Bronchodilator (theophylline)	Induction of CYP3A4 and/or CYP1A2 and/or CYP2E1	Decreased drug bioavailability
Anaesthetic (fentanyl, propofol, sevoflurane)	Induction of CYP2E1	Sedation
Antimicrobial (voriconazole)	Induction of CYP3A4 and/or CYP2C9 and/or CYP2C19	Decreased drug bioavailability
Anticoagulant (phenprocoumon, warfarin)	Induction of CYP3A4 and/or CYP2C9	Decreased drug bioavailability
Hypnotic (alprazolam, midazolam, zolpidem); Tricyclic antidepressant (amitriptyline, nortriptyline); Cardiovascular (nifedipine)	Induction of CYP3A4 and/or CYP2C19	Decreased drug bioavailability
Gastrointestinal (esomeprazole, omeprazole, pantoprazole); Hypoglycaemic (gliclazide, tolbutamide)	Induction of CYP2C19	Decreased drug bioavailability
Opioid analgesic (dextromethorphan, methadone, oxycodone, pethidine)	Induction of CYP3A4 and/or CYP2D2	Decreased drug bioavailability
Anxiolytic (buspirone); Smoking cessation (bupropion); Antimigraine (eletriptan, naratriptan, rizatriptan, zolmitriptan); Selective serotonin reuptake inhibitor (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline); Serotonin and noradrenaline reuptake inhibitor (nefazodone, venlafaxine)	Additive effect on serotonin signalling	Serotonin syndrome, lethargy
Antidiarrheal (loperamide)	Unknown	Delirium

exerted hepatoprotective activity (Bayramoglu et al. 2014).

Toxicity and safety

Only 2% is the estimated rate of HYP associated adverse drug reactions; typically including gastrointestinal irritations (0.6%), allergic reactions (0.5%), fatigue (0.4%) and restlessness (0.3%). However, as a precautionary measure, use of HYP products is not recommended for patients having history of mania or psychosis. Since, subcutaneous administration of HYP showed dose-dependent gastric irritation in rodents; co-administration of HYP with non-steroidal anti-inflammatory drugs is not advised. Sunlight exposure following topical application of HYP oil is also reported to cause the reversible skin irritation. Although, most clinical trials concluded HYP to be safe for mother as well as infant during pregnancy and lactation, caution is warned against simultaneous drug therapy owing to possibility of herb–drug interaction (Abdel-Salam 2005; Langer 2009). Such precautionary information should be included in the product-label (Clauson et al. 2008).

Herb–drug interactions

H. perforatum is well tolerated as a monotherapy, but clinical herb–drug interactions are witnessed on co-administration of other pharmaceuticals. Phytoconstituents of HYP are said to stimulate pregnane X-receptor mediated induction of intestinal CYP3A4 and P-gp, which reduces bioavailability of CYP3A4/P-gp substrates. Other commonly HYP modulated CYP isoenzymes include 2E1, 2C9 and 2C19. Hypericin, hyperforin and flavonoids are inexplicitly said to be the interacting molecules, while aristoforin also demonstrates the same (Mannel 2004; Nowack 2008; Rahimi and Abdollahi 2012; Semelakova et al. 2016). Although the herb–drug interactions are generally observed with chronic HYP treatment and not with acute (Borrelli and Izzo 2009), concomitant administration of HYP and drugs enlisted in Table 3 should be avoided.

Conclusion

The clinical outcomes encourage long-term monotherapy of HYP in mild to moderate depression; but, HYP in co-therapy with synthetic antidepressants is not recommended owing to the occurrence of serotonin syndrome. Inherent wound healing effect of HYP is seen to potentiate with appropriate pharmaceutical amalgamations. Pharmacological activities of HYP appear correlated through the integrated mechanisms, antioxidant activity being core of the most. Recently found therapeutic effects of HYP against psychiatric, metabolic and neoplastic disorders open doors to whole new unexplored areas, especially in clinical research. Also, synthetic drug development from herbal leads of HYP seems rewarding, aristoforin being an excellent example of the same. Lastly, safe usage measures of this commonly-over-the-counter product (HYP) should be communicated well by suitable product-labelling.

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