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Review article

Medicinal plants' proposed nanocomposites for the management of endocrine disorders☆

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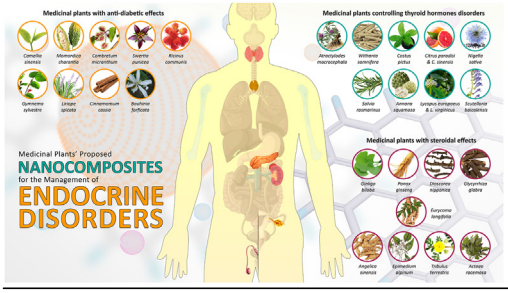
GRAPHICAL ABSTRACT



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ABSTRACT

Extensive attention has been focused on herbal medicine for the treatment of different endocrine disorders. In fact, compelling scientific evidence indicates that natural compounds might act as endocrine modulators by mimicking, stimulating, or inhibiting the actions of different hormones, such as thyroid, sex, steroidal, and glucose regulating hormones. These potentials might be effectively employed for therapeutic purposes related to the endocrine system as novel complementary choices. Nevertheless, despite the remarkable therapeutic effects, inadequate targeting efficiency and low aqueous solubility of the bioactive components are still essential challenges in their clinical accreditation. On the other hand, nanotechnology has pushed the wheels of combining inorganic nanoparticles with biological structures of medicinal bioactive compounds as one of the utmost exciting fields of research. Nanoparticle conjugations create an inclusive array of applications that provide greater compliance, higher bioavailability, and lower dosage. This can safeguard the global availability of these wealthy natural sources, regardless of their biological occurrence. This review inspects future challenges of medicinal plants in various endocrine disorders for safe and alternative treatments with examples of their nanoparticle formulations.

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1. Introduction

Nowadays endocrine disorders have become a more prevalent complex global health problem which increases the economic burden on governments worldwide due to their serious complications. According to a recent study published in 2020, 10% of the worldwide population are suffering from diabetes mellitus, around 5% suffers from hypothyroidism, 0.2–1.3% are affected by hyperthyroidism, in addition to more than 200 million females are diagnosed with osteoporosis (Pal and Bhadada, 2020).

On the other hand, although the therapeutic agents managing endocrine disorders are overlooked, they are vital elements within the protective measures for patients suffering from diabetes mellitus, thyroid disorders, infertility, and adrenal gland diseases. In addition to the conventional approaches in this field, medicinal plants acquire exceptional consideration from professionals to develop potent phytomedicine for optimizing curative outcomes. Therefore, the rising interests of researchers in nutrition and natural products are fast rising to the frontier of research priorities.

Herein, this review provides examples of the most effective medicinal plants used for the management of common endocrine diseases taking into account the green-formulated nanoparticles, which are more effective than the crude extracts. Their higher efficacy can be attributed to their higher surface area and better solubility, which in turn enhance the therapeutic activity and thus overcome the limitations of insolubility, low bioavailability, and incapability to reach their sites of action (Desai et al., 2012). A profound summary about these medicinal palnts, their active constituents, and reported nanoformulations can be found in Table S1 (Supplementary Materials).

2. Medicinal plants with antidiabetic effects

Currently, diabetes mellitus (DM) is a global public concern and the ground behind a major disease-economic burden due to its association with numerous health-related complications such as diabetic neuropathy, renal failure, and peripheral vascular disease (Saeedi et al., 2019). This complex metabolic disease demands multiple pharmacological treatment approaches. Consequently, a variety of medicinal plant supplements are gaining consideration in diabetes management, along with the increasing interest in metals for improving glucose metabolism. This has encouraged scientists to optimize the antidiabetic effects of specific medicinal plants by formulating them with metals such as zinc and silver (Umrani and Paknikar, 2014). This expansion of nanotechnology in herbal medicine has unravelled new landscapes for diabetes therapy.

2.1. Camellia sinensis *(tea plant)*

Camellia sinensis, also known as the tea plant, has been widely investigated due to its potential pharmacological properties such as antiobesity, anticancer, antibacterial, and antioxidant effects (Luo et al., 2020), as well as antidiabetic activity. These pharmacological and biological activities of *C. sinensis* have been attributed to the polyphenolic flavonoid content of the plant, such as catechins (Spadiene et al., 2014).

The antidiabetic effect of the isolated compounds and extracts of *C. sinensis* has been established at the *in vitro* and *in vivo* levels. *In vitro,* it showed inhibition of α-glucosidase and α-amylase in cultured cells, such as HepG2 and mouse 3T3-L1 pre-adipocytes cell lines, specifically achieving 99% of α-glucosidase inhibition (Sánchez et al., 2020). *In vivo*, oral administration of the leaves extracts established anti-hyperglycaemic, anti-hyperlipidaemia and anti-hyperproteinaemia effects in a streptozotocin-induced diabetic mice model (Al-Attar and Zari, 2010) Likewise, the oral administration of *C. sinensis* tea has caused anti-hyperglycaemic and anti-hyperlipidaemia activities in diabetic rats (Haidari et al., 2013).

On the other hand, clinical studies revealed that the extract of *C. sinensis* is beneficial for diabetic individuals, especially those with a shorter duration of the disease by maintaining their well-being and increasing their level of performance. However, this extract was ineffective in acute diabetic complications (Spadiene et al., 2014).

It is also worth mentioning that the anti-thyroidal properties of the flavonoids compounds in this plant which were declared to have improved the hypertrophy of thyroid follicles and elevated Na^+/K^+-ATPase, as well as inhibiting thyroid peroxidase (TPO), and blocking 5'-monodeiodinase, in addition to decreasing the serum levels of triiodothyronine (T_3), and thyroxine (T_4) by increasing the serum concentrations of thyrotropin (TSH) (Parimal et al., 2020).

Furthermore, the formulation of *C. sinensis* extract with green zinc oxide nanoparticles (ZnO NPs) exhibited a protective effect against renal, hepatic, testicular, and pancreatic toxicity of monosodium glutamate (MSG) in rats, indicating the potent capability of this formulation as an antidiabetic agent via its actions of inhibiting lipid peroxidation, amplifying antioxidant parameters, reducing glucose levels, and improving insulin secretion from pancreatic islets of Langerhans (Hamza et al., 2021).

2.2. Momordica charantia *(bitter melon)*

Momordica charantia, commonly identified as balsam pear, bitter gourd, melon, or karela is well known for alleviating diabetes (Joseph and Jini, 2013). The active compound which is mainly responsible for the antidiabetic effect of this plant is charantin (Grover and Yadav, 2004). *In vitro* investigation suggested that polypeptide K and seed oil from *M. charantia* have a potent hypoglycaemic effect. These two components significantly inhibited the α-glucosidase and α-amylase enzymes (Ahmad et al., 2012).

Alloxan stimulates hyperglycaemia in animal models by its selective cytotoxicity on the pancreatic β-cells through oxidative stress caused by the generation of free radicals (Gandy et al., 1982). According to a recent *in vivo* study, the aqueous extract of *M. charantia* pulp demonstrated significant alleviation of alloxan-induced diabetes in rats, indicating potent anti-hyperglycaemic and anti-oxidative effects of this extract. Vital organs such as the kidneys and the heart were not affected by the damage triggered by oxidative stress in this animal model. This protective effect was attributed to the anti-oxidative activity of *M. charantia* components. Moreover, the methanolic extract of *M. charantia* leaves has shown an antidiabetic effect in rabbits (Salehi et al., 2019).

Furthermore, in a clinical study carried out in 1999, the suspension of *M. charantia* pulp significantly reduced the postprandial serum glucose in 86% of moderate non-insulin-dependent diabetes mellitus (NIDDM) patients samples and lowered the fasting glucose in 5% of these patients (Ahmad et al., 1999). More importantly, the formulation of *M. charantia* with zinc oxide nanoparticles and silver nanoparticles has augmented their antidiabetic activity in streptozotocin-induced diabetic male Wistar rats compared with the crude extract (Shanker et al., 2017).

2.3. Combretum micranthum *(kinkéliba)*

Combretum micranthum is a widely traditionally used medicinal plant in West Africa and is indicated as an antidiabetic, anti-hypertensive, anti-inflammatory, anti-malarial, and hepatoprotective agent (Kpemissi et al., 2020).

The antidiabetic effect of this plant is attributed to the polyphenols which represent the active ingredients in this plant (Chika and Bello, 2010). A noteworthy *in vivo* and *in vitro* antidiabetic study of these polyphenolic compounds has shown their ability to inhibit glucose production and the PEPCK mRNA expression in H4IIE rat hepatoma cell line (Welch et al., 2018). Furthermore, an *in vivo* study reported that *C. micranthum* aqueous leaf extract has significant antidiabetic activity against both types of diabetes, suggesting that this extract might play a role in enhancing insulin secretion. The outcomes of the same study revealed that *C. micranthum* aqueous leaf extract was better than glibenclamide in reducing blood glucose in diabetic rats, which might be

attributable to an additional extra-pancreatic pathway (Chika and Bello, 2010).

However, the complex of this plant extract with silver sulphide nanoparticles was only investigated for antimicrobial effects, and it has revealed promising results (Sibiya and Moloto, 2018). Therefore, it is expected in the near future to have novel nanotechnology applications that might potentially have antidiabetic effects.

2.4. Swertia punicea *(felwort)*

Swertia punicea is part of the traditional Chinese medicine (TCM) system component, also known as "Zi Hong Zhang Ya Cai", formulated with other medicinal plants to treat various diseases. Around 78 active compounds from different classes (triterpenes, iridoids, xanthones, and sterols) were isolated from this plant. Most of the compounds were established to have antidiabetic effects, alleviate oxidative stress, and inhibit hepatic fibrosis and cirrhosis (Zafar and Wang, 2018).

The active compounds responsible for this plant's hypoglycaemic activity of this plant are methylswertianin and bellidiflorin (Tian et al., 2010). Treatment with these compounds has demonstrated reduced fasting blood glucose, increased hepatic glycogen rates, increased hepatic glucose uptake, and decreased hepatic glucose release by decreasing the G6Pase activity on top of increasing the GK activity in the liver. More interestingly, they improve insulin resistance by enhancing insulin signalling pathways, increasing in InsR-α, IRS-1, and PI3K levels of expression. Furthermore, they led to improvements within the lipid profile in the animal model, which suggested protective effects against cardiovascular complications that might result from type-2 diabetes. Hence, *S. punicea* could be a potential candidate for the treatment of type-2 diabetes (Li et al., 2017; Tian et al., 2010).

Moreover, swertiamarin, the seco-iridoid glycoside has recently received extensive research interest due to its antidiabetic effect mediated by elevating both PPARγ/GLUT-4 and adiponectin mRNA, upregulating GLUT-2, inhibiting the α-glucosidase enzyme, and reducing oxidative stress as well as insulin resistance (Fadzil et al., 2021). More importantly, swertiamarin has been recently exposed to nanotechnology by amino-functionalized graphene oxide formulation using ultrasonication to be evaluated as an anticancer agent. This nanoformulation potentially enhanced the stability and hemocompatibility of the bioactive compounds without disturbing the medicinal properties (Gayathri, 2021). Clearly, the same formulation might have antidiabetic potential.

2.5. Ricinus communis *(castor oil plant)*

Ricinus communis, also known as the castor plant, is widely used in traditional medicine for its potential activity against oxidative stress, allergy, analgesic, hepatoprotective, anti-inflammatory, and antidiabetic effects (Jena and Gupta, 2012).

The ethanolic extract of castor oil plant roots contains an array of potent phytochemicals responsible for antidiabetic effects, such as terpenes, alkaloids, flavonoids, saponins, phenolic compounds like gallic acid, kaempferol, rutin, thujone, ricin, ricinoleic acid, lupeol, pinene, and gentisic acid. This extract has shown a remarkable therapeutic effect as an antidiabetic agent in alloxan-induced diabetic rats by reducing the fasting blood glucose to almost normal levels and elevating insulin levels, as well as improving the lipid profile to minimize the risks of diabetic-related vascular diseases (Abdul et al., 2018). It is also noteworthy that the 50% ethanolic extract of *R. communis* roots was effective in increasing the uptake of blood glucose, mostly by the survival of pancreatic beta cells. Furthermore, it reversed the diabetes-induced damage to the kidneys and liver in the animal model. These effects are credited to the protective role of *R. communis* in trapping free radicals that usually destroy pancreatic cells (Shokeen et al., 2008).

Nanotechnology was also applied to this plant to amplify its pharmacological effects. According to a recent study in 2020, the methanolic extract of *R. communis*, which was subjected to synthesizing gold nanoparticles (Au-NPs), has shown significant improvement in antibacterial activity compared with the normal methanolic extract (Rahman et al., 2021). Therefore, similar further trials for investigating the nanoparticle formulations of *R. communis* against diabetes are expected.

2.6. Gymnema sylvestre *(australian cowplant)*

Gymnema sylvestre has been used traditionally in ayurvedic medicine for managing diabetes and other metabolic disorders such as dyslipidaemia (Marakis et al., 2018).

The various *G. sylvestre* extracts in different solvent systems such as ethanolic, methanolic, aqueous and acetone extracts were reported to improve diabetes by suppressing body weight gain, reducing plasma glucose levels, improving lipid profile, and inhibiting fat accumulation in epididymal adipose tissue and liver. The leaves of this plant contain gymnemic acids: a mix of around 17 different saponins, anthraquinones, and acidic glycosides. Moreover, the antidiabetic effect of those isolated and purified gymnemic acids has been well established (Pothuraju et al., 2014). It was found that the molecules of gymnemic acids have very similar structures to that of the glucose molecule, and can delay intestinal absorption of glucose. Therefore, they can antagonize glucose by binding to its receptors located on the tongue taste buds and prevent the activation of these receptors by the sugar molecules, thereby inhibiting sugar uptake (Sahu et al., 1996), in addition to their binding to Na^{+}-glucose symporter in the intestine to prevent glucose absorption (Pothuraju et al., 2014). Moreover, gymnemic acids can increase pancreatic insulin secretion by enhancing the regeneration of pancreatic islet cells, which in turn increases the utilization of glucose via the insulin-dependent pathway (Nakamura et al., 1999).

Furthermore, The antidiabetic properties of *G. sylvestre* are also attributed to terpenoids, flavonoids and coumarins, in addition to other secondary metabolites such as glutamic acid and arginine (Marles and Farnsworth, 1995).

Additionally, a recent study related to nanotechnology reported that the methanolic extract of *G. sylvestre*, combined in a nanoparticle formulation with dried potato starch as a vehicle, has potentially optimized the antidiabetic properties of the plant extract (Varadharaj et al., 2020).

2.7. Liriope spicata var. prolifera *(lilyturf)*

The tuberous root of this medicinal plant has been extensively used as antidiabetic therapy in traditional Chinese medicine (Liu et al., 2013). Moreover, the hypoglycaemic properties of the water extract and crude polysaccharides extracted from the tuberous root of *L. spicata* var. *prolifera* were reported in normal mice and type-2 diabetes induced by streptozotocin (Chen et al., 2009; Xiao et al., 2014). This water extract inhibited hepatic damage, which is usually caused by streptozotocin, increased the activity of glucokinase (GK), glycogen content, and glycogen synthetase (GS), and prevented the increase of glycogen phosphorylase (GP) and glucose-6-phosphatase (G6Pase) activities in hepatic cells. It also downregulated the expression of glycogen synthase kinase-3β and upregulated the hepatic expression of glucose transport protein-4, phosphoinositide 3-kinase, insulin receptor substrate-1, insulin receptor, and protein kinase B (Fang et al., 2018; Xiao et al., 2014). Furthermore, *L. spicata* polysaccharides had decreased both fasting blood glucose and glycosylated haemoglobin; it also exhibited potential protective properties against diabetic nephropathy induced in diabetic rats, in addition to normalizing hyperlipidaemia, ameliorating oxidative stress, and reversing the structural damages in kidney tissue (Xiao et al., 2013).

It is confirmed that those natural polysaccharides are positioned as consistent antioxidants due to their scavenging ability for the free radicals more effectively and more safely compared with synthetic antioxidants (Yan et al., 2013). Interestingly, a recent study has confirmed the

importance of the polysaccharides extracted from *L. spicata* and other medicinal plants as essential bioactive macromolecules against diabetes.

Nanoformulations were developed whereby these natural polysaccharides are employed in managing diabetes. Indeed, a nanoformulation using a selenylated polysaccharide (Se-MCPIIa-1) was reported to have potential effects in intensifying the hypoglycaemic effect (Ru et al., 2020).

2.8. Cinnamomum cassia *(Chinese cinnamon)*

Cinnamomum cassia which is also recognized as Chinese cinnamon or Chinese *cassia* is a very well-known antidiabetic plant. This pharmacological effect was investigated *in vitro* and established that cinnamaldehyde isolated from *C. cassia* bark is a potent antidiabetic agent by inhibiting the rat lens aldose reductase (Lee, 2002). On the other hand, water extract of cinnamon was reported for its significant hypoglycaemic properties, alone and in combination with glibenclamide, in alloxan-induced diabetic rats, showing that the combination therapy was more effective in decreasing blood glucose levels. This therapeutic effect is thought to be caused by the active phytochemicals in this plant such as saponins, alkaloids and flavonoids (Kamble and Rambhimaiah, 2015), in addition to cinnamic acid, methyl hydroxychalcone polymer and polyphenols (Sangal, 2011).

The antidiabetic effect of *C. cassia* silver nanoparticles was also investigated in the streptozotocin diabetes animal model and has shown remarkable antioxidant therapeutic properties that have attenuated and reversed the damage induced by streptozotocin in diabetic rats (Koffi Kouame et al., 2019).

In addition, nano silver/gold formulation of aqueous extracts has exhibited a remarkable reduction in body weights, glucose levels, and insulin resistance, as well as demonstrating a potent anti-hyperglycaemic effect in streptozotocin-induced diabetic rats (Elobeid, 2016).

2.9. Bauhinia forficata *and* Bauhinia variegata *(orchid trees)*

Bauhinia forficata has been traditionally used for the treatment of type-2 diabetes mellitus owing to its hypoglycaemic and antioxidant properties that are mainly attributed to the flavonoids, the main active compounds in this plant (Cechinel-Zanchett et al., 2018). Furthermore, according to a recent study carried out in 2020, ethanol extract of *B. forficata* has been established to be effective in managing postprandial hyperglycaemia, hyperlipidaemia, glycation, and oxidative stress in type-2 diabetes mellitus, with excellent inhibitory effects for α-glycosidase, α-amylase, and lipase enzymes (Franco et al., 2020).

On the other hand, ethanolic extract of *Bauhinia variegata*, known as Kachnar, significantly reduced oxidative stress, blood glucose, triglyceride, cholesterol, LDL, VLDL, and increased the HDL (Tripathi et al., 2019). These antidiabetic, antioxidant, and anti-hyperlipidaemia effects were confirmed and compared with the gold nanoparticles-incorporated extract in streptozotocin-induced diabetic rats. It was concluded that the Au-NPs formulation of *B. variegata* was more potent as an antidiabetic agent by reversing the damage in pancreatic β-cells owing to the high antioxidant and anti-hyperlipidaemia activities in comparison to the extract alone (Abdel-Halim et al., 2020).

3. Medicinal plants with steroidal effects

Steroidal hormones are endogenously classified into two key groups mostly produced by the adrenal gland: the first group includes corticosteroids (mineralocorticoids and glucocorticosteroids) whereas the second group contains the sex hormones (estrogenic and androgenic hormones). The steroidal or anti steroidal effects of any medicinal plant are typically mediated by interrupting the steroid synthesis pathway, interfering with the activity of steroidogenic enzymes or steroid receptors (Fung and Linn, 2017).

3.1. Glycyrrhiza glabra *(licorice)*

Glycyrrhiza glabra is a widely used herb for its beneficial effects on health. The active compound in this plant is glycyrrhizin. It increases cortisol levels in the body by preventing its inactivation by the 11β-hydroxysteroid dehydrogenase enzyme. These elevated cortisol levels will bind to the mineralocorticoid receptors leading to hyper mineralocorticoid-like effects such as fluid retention, hypertension, and hypokalaemia (Isbrucker and Burdock, 2006). However, according to the World Health Organization, the safe daily dose of this plant is 100 mg/day (WHO Technical Report Series, 2005). It is hypothesized that liquorice root extract might be beneficial as an adjunctive treatment for different disorders caused by mild cases of adrenal insufficiency, as well as low aldosterone output, and correcting hyperkalemia induced by spironolactone treatment in polycystic ovary syndrome. Moreover, *glycyrrhiza* therapy can be used in patients suffering from orthostatic hypotension by improving potassium levels, and blood volume, as well as preventing the activation of baroreceptors (Stansbury et al., 2012).

Another bioactive component obtained from *G. glabra* is a triterpentine saponin called glycyrrhizic acid. It has a moderate anti-inflammatory effect and potency that is generally less than dexamethasone, prednisolone, diclofenac, and indomethacin (Kumagai et al., 1957). However, its therapeutic potential is limited since it has low bioavailability due to poor water solubility (Sui et al., 2012). This problem was solved by formulating the glycyrrhizic acid in polymeric nanoparticles by loading it on chitosan-katira gum. As a result, the anti-inflammatory effect was maximized and bioavailability for oral administration was significantly improved (Bernela et al., 2016).

Moreover, the protective effects of *G. glabra* against testicular dysfunction and oxidative stress induced by methotrexate (MTX) were confirmed by ameliorating the toxicity of MTX on albumin, total proteins, and globulins as well as biomarkers that are related to oxidative stress. Not only that, *G. glabra* also prevents reduction in serum testosterone and inhibits the rise of IL-6 and IL-1β, as well as inhibiting sperm abnormalities and reducing MTX-induced sperm mortality. Additionally, *G. glabra* prevented the upsurge in testis immunoreactivity for cyclogenase-2 and Bcl-2-associated X protein. It also upregulated the steroidogenesis gene expression which is suppressed by MTX, and amplified antioxidant enzymes such as glutathione peroxidase, and catalase, along with reducing oxidative stress biomarkers such as inflammatory cytokines and testicular malondialdehyde (Aldhahrani et al., 2021). Furthermore, this plant is now recommended for the treatment of estrogen-dependent ailments such as endometriosis, breast cancer, premature ovarian failure, and polycystic ovary syndrome, due to the presence of many phytoestrogens such as licuraside, licochalcon A/B, ferulic acid, mangiferin, shaftoside, glabron, glycycumarin, neoisoliquiritin, glycyrrhizin, licoflavonol, isoliquiritigenin, licoflavon, glycyrrhisoflavon, liquiritigenin, glycyrol, formonetin, isoviolanthin, liquiritin, and glycyrrhetinic acid (Akbaribazm et al., 2021). Therefore, this effect might be optimized by using the same nanotechnology for infertility treatment in both male and female.

3.2. Dioscorea nipponica

The rhizome of *Dioscorea nipponica* is traditionally used in China for the treatment of leg and lumbar pain, and for the management of rheumatoid arthritis (Ou-Yang et al., 2018). It contains a natural steroidal saponin known as diosgenin. The structure of this compound is similar to the glucocorticoid structure. It inhibits the inflammation induced by allergens in the intestine and trachea through the binding to glucocorticoids receptors, suppressing the secretion of IL-6, IL-1b, and TNF-α, and upregulating of glucocorticoid-induced leucine zipper (GILZ), glucocorticoid receptor (GRs), the secretory leukocyte protease inhibitor (SLPI), tristetraprolin (TTP), and mitogen-activated protein kinase phosphatase-1 (MKP-1), in addition to the downregulation of NF-κB (Junchao et al., 2017). Diosgenin is also found in *Dioscorea bulbifera*, and its

nanoparticle formulation with functionalized iron oxide was reported to be effective against breast cancer via its anti-proliferative effects. Therefore, it was highly recommended as a potent combinatorial nanomedicine with metallic magnetic nanoparticles due to the greater effect of the synergistic combination that guarantees higher therapeutic activity at lower doses (Ghosh et al., 2015).

3.3. Panax ginseng *(Korean ginseng)*

Ginseng saponins (ginsenosides) are the main active constituents of *Panax ginseng*. These compounds can activate glucocorticoid receptors (Leung et al., 2007). Therefore, it is used in the treatment of frequent inflammatory diseases due to its anti-inflammatory properties. Those properties were confirmed with purified ginsenosides, such as ginsenosides Rg1, Rb1, Rh2, and Rg3, as well as compound K. Both downregulations of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, as well as the reduced expressions of COX-2 and iNOS enzymes are underlying the anti-inflammatory effect of ginsenosides in microglia and M1-polarized macrophages. Additionally, the pro-resolution effect of ginsenosides on inflammation derived via M2-polarized macrophages contributes to inhibiting the inflammatory process and enhancing inflammation resolution (Im, 2020). This anti-inflammatory effect of *P. ginseng* was optimized via formulating the leaves extract with Au-NPs gold nanoparticles. This formulation showed a remarkable suppression of the activation of NF-κB in the macrophages, and downregulation of the inflammatory mediators such as TNF-α, prostaglandin E2 (PEG2), nitric oxide (NO), and IL-6, in addition to inhibiting the activation of NF-κB signalling pathway by lipopolysaccharide through p38 mitogen-activated protein kinase (MAPK) (Ahn et al., 2017).

Moreover, the phytoestrogenic effect of ginsenoside-Rh1, a ginseng saponin from *P. ginseng* was established through activating and binding to the estrogenic receptors (Lee et al., 2003). Furthermore, ginsenoside-Rb1, another compound isolated from *P. ginseng* possessing estrogenic activity, has a regulatory effect on adrenal tyrosine hydroxylase that is recognized to be interrelated to estrogen regulation. This ginsenoside-Rb1 has also shown a stimulatory effect for both estrogen receptors α and β, leading to transactivation of the estrogen-receptive genes. However, this activation happened without direct receptor binding (Cho et al., 2004). Besides, in a recent study, nanoparticle conjugation formulation of glycol chitosan-coated with selenium nanoparticles was found to be effective in enhancing and increasing the proportion of Rb1 in *P. ginseng* root extract (Abid et al., 2021). Accordingly, this formula might be effective in the treatment of diseases that results from the lack of estrogenic activity such as infertility, osteoporosis, and Alzheimer's disease.

3.4. Ginkgo biloba

Ginkgo biloba is a well-known plant commonly used in obesity, diabetes, hypertension, and other metabolic disorders (Fang et al., 2020) and has anti-estrogenic effects. It contains a mixture of around 300 active components; 24% are flavonoids while 6% are terpene lactones. The inhibitory effects of the flavonoid compound "kaempferol" on aromatase enzyme mainly lead to estrogen biosynthesis suppression. Therefore, it was suggested that those flavonoids could potentially be used as adjuvant therapy in the treatment of breast cancer by decreasing estrogen levels without causing an estrogen depletion which might occur with the application of conventional medicine (Park et al., 2015). More interestingly, *G. biloba* extract was found to have a biphasic effect on estrogen. Therefore, it is highly recommended to be used as a hormone replacement therapy (HRT) instead of exogenous estrogens to avoid their undesirable adverse effects, such as the high risks of breast cancer and irregular bleeding (Oh and Chung, 2006).

Furthermore, *G. biloba* extract has inhibited aluminum neurotoxicity (Abd-Elhady et al., 2013), and diminished stress-induced memory disorders in rats (Walesiuk et al., 2005). Consequently, it has been considered as a memory enhancer (Verma et al., 2019). On the other hand, *G. biloba* extract formulated with silver nanoparticles has exhibited promising antibacterial results (Huang et al., 2020) which can open new doors for investigating the therapeutic effects of this formula against breast cancer, memory loss, and as an effective choice for HRT.

3.5. Actaea racemosa *(syn. Cimicifuga racemose; black cohosh)*

Actaea racemosa is commonly used in America, Asia, Europe, and Australia for many health ailments in the female, especially those who are suffering from polycystic ovary syndrome to manage the side effects of conventional hormonal therapies, and it has a modulatory effect on steroidogenesis (Azouz et al., 2021).

The low doses of the active constituents of this plant extract are considered potent phytoestrogens. However, they do not affect the mammary gland and uterus. Instead, they mimic the neurotransmitters in the hypothalamus such as dopamine, noradrenaline, serotonin, and GABA; hence, might be effective against menopausal symptoms and a substitutional choice as a HRT candidate without showing adverse estrogenic complications (Wuttke et al., 2014). The extract of this plant was also formulated with silver nanoparticles and demonstrated to be a potent antibacterial agent (Okafor et al., 2013), and so the effect of this nanoparticle formulation is highly recommended to be considered as HRT.

3.6. Tribulus terrestris *(bindii)*

Tribulus terrestris, also known as *Tribulus*, goat head, and hard thorns, is commonly used as a sexual stimulant. *T. terrestris* grows in deserts, subtropical, and Mediterranean areas (Ghanbari et al., 2021). Several compounds with many biological activities have been isolated from *T. terrestris*, especially flavonoids, steroidal saponins, alkaloids, and polyphenol carboxylic acids (Stefănescu et al., 2020).

Animal studies demonstrated that the plant extract enhanced sexual function by elevating the testosterone levels and controlling the NF-κB and Nrf2/HO-1 pathways (Sahin et al., 2016). The *T. terrestris* steroidal saponins are thought to elevate the endogenous testosterone via an indirect action mediated by the LH-type effect or the weak androgenic agonistic effect (Sanagoo et al., 2019). Moreover, protodioscin, a steroidal saponin that is considered the main active compound of *T. terrestris,* is responsible for improving the ovarian and uterus histological features of polycystic ovary syndrome in women. In addition to stimulating sexual desire in postmenopausal syndrome, this has a significant therapeutic effect on breast and ovarian cancers (Ghanbari et al., 2021).

In terms of the nanoformulation of this plant extract, it was only investigated as an antibacterial agent. For example, both silver and gold nanoparticles formulations of *T. terrestris* have shown excellent antibacterial potentials and are recommended for diagnostic and therapeutic targets in the future (Hamidi et al., 2019; Molani et al., 2021). Hence, the green synthesis application on *T. terrestris* should be investigated in the field of polycystic ovary syndrome, postmenopausal syndrome, and breast and ovarian cancers.

3.7. Epimedium *alpinum (horny goat weed)*

Epimedium is a common medicinal plant that has been indicated for osteoporosis. Its estrogenic effects result from many phytoestrogens, such as flavonoids, steroids, and lignans (Xu et al., 2016). It has been shown that *Epimedium's* flavonoids counteract the inhibition of the hypothalamic-pituitary-adrenal (HPA) axis caused by glucocorticoids via adrenocorticotropic hormone (ACTH) as well as insulin-like growth factor-II (IGF-II) pathways and thus enhancing the renaissance of the adrenal cortex (Huang et al., 2013). Icariin and icariside-II are the main pharmacologically active constituents of this plant. Icariin can efficiently stimulate estradiol (E2) synthesis and promote ovarian development in

mammalians by increasing aromatase expression in ovaries via CREB/PKA/cAMP pathways (Zheng et al., 2020). However, the nano-formulation research work related to this plant was only applied to providing a consistent procedure for evaluating the metabolites of its flavonoids in complex biological samples by extracting its activated glycosides *in vivo* and *in vitro* (Zhang et al., 2020).

3.8. Angelica sinensis *(female ginseng)*

Angelica sinensis is a famous plant in traditional Chinese herbal medicine, effectively used in the management of osteoporosis, and found to be a potent promoter for bone formation through the GPR30/EGFR pathway (Yang et al., 2019). GPR30 is considered an innovative membrane estrogen receptor, involved in the non-genomic estrogen pathway having a vital role in osteoblast differentiation and proliferation (Khan et al., 2015). Ligustilide is the foremost active component in *A. sinensis*. This compound has been suggested as an effective therapeutic agent for healing osteoporosis and increasing bone mass by activating the G protein-coupled estrogen receptor/epidermal growth factor receptor (GPR30/EGFR) signalling through the enhancement of osteoblast differentiation and prevention of peroxidative damage (Yang et al., 2019). However, the bioavailability of the natural benzoquinone, ligustilide, is relatively poor due to the first pass effect (Xie et al., 2020).

Nevertheless, to improve its oral bioavailability and stability, a previous study has applied the nanotechnology approach to this compound by formulating it as a complex with hydroxypropyl-β-cyclodextrin. This optimized formula became more stable against light and temperature and exhibited higher plasma concentration in rats due to the enhancement of ligustilide bioavailability. These promising results might have great potential in the future, perhaps by encouraging further pharmaceutical formulations (Lu et al., 2014).

3.9. Eurycoma longifolia *Jack (tongkat ali)*

Eurycoma longifolia Jack is found on slopes of the hilly lands of the Malaysian tropical forests and is widely used as a supplement for improving sexuality and fertility for males (Tambi and Imran, 2010). Both animal and human trials have reported the beneficial effects of *E. longifolia* root extracts in the management of male fertility (Rehman et al., 2016). It was recommended as a testosterone promoter for managing late-onset hypogonadism in men (Tambi et al., 2012). Moreover, eurycomanone, a major active constituent of the plant extract, has shown a significant effect on the hypothalamic-pituitary-gonadal axis, leading to a potential improvement in rat spermatogenesis (Low et al., 2013b). This compound was further suggested as a novel therapeutic choice for testosterone-deficient idiopathic male infertility owing to its the ability to elevate the production of testosterone and enhance testosterone steroidogenesis by blocking the aromatase transformation of testosterone to estrogen (Low et al., 2013a). However, eurycomanone has a short half-life in blood circulation after intravenous and oral administration. Therefore, it has been complexed with chitosan polymer to decrease the dosage and improve its bioavailability, revealing that this compound acts as an aromatase blocker and can be efficiently used in male infertility. Moreover, the impact of eurycomanone nanoformulation with chitosan has shown a sharp increase in the transcription level of FSH and LH, progesterone, and testosterone, with a significant decrease in serum 17β-estradiol (Bhat et al., 2019).

4. Medicinal plants controlling thyroid hormones disorders

In addition to the various ailments and physiological disorders that can disturb the balance of thyroid hormones, it is good to highlight that continuous exposure to specific environmental factors such as pesticides, herbicides, fungicides, and insecticides are considered serious risk factors for triggering thyroid diseases. This is due to the disruptions in the endocrine system, inhibition of thyroidal iodine uptake, interference in thyroid hormone receptors, blockage in transport proteins, interruptions in iodothyronine deiodinases activity, acceleration in thyroid hormone clearance, weakening the thyroid hormone uptake and its activity in the target cells (Nagarathna and Jha, 2013).

Hence, researchers are currently highly attentive to phytochemicals which act as natural thyroid hormone analogs or even as modulators for the nuclear receptors, to replace or support synthetic compounds. This exploration of agonists, antagonists, ligands, co-repressors, and co-activators components is a promising therapeutic target for managing thyroid disorders (Taïbi et al., 2021). Moreover, it has been recommended to be utilized as a concoction of natural products in combination with chemical drugs, in order to optimize the therapeutic effects (Abderrahim et al., 2019).

4.1. Nigella sativa *(black seed)*

Nigella sativa is the furthermost medicinal plant cited as an anti-hypothyroidism agent, owing to the main bioactive ingredient of its essential oil thymoquinone. According to a recent animal study, this mixture of essential oils might be beneficial as adjuvant therapy for improving thyroid hormone levels by reducing oxidative stress due to the potent antioxidant effect of thymoquinone. This compound is responsible for normalizing the abnormalities of thyroid hormones in both hypothyroidism and hyperthyroidism models. It has significantly amplified the total antioxidant capacity, reduced nitric oxide, and elevated total triiodothyronine (TT3) levels in hypothyroidism. On the other hand, it has declined TT3 levels in the hyperthyroidism animal group (Avci et al., 2021). Besides, another recent study reported that this essential oil's therapeutic effects against thyroid damage were induced by aluminum chloride. Treatment with *N. sativa* seed oil has facilitated stimulating the regeneration of the epithelial cells surrounding the thyroid gland follicles, and improved TT3 levels as well as the histological features of the thyroid gland impaired by aluminum chloride (Mekkey, 2021).

It was also reported that the daily consumption of *N. sativa* was effective against hypothyroidism in Hashimoto's thyroiditis patients due to the potent antioxidant properties of this plant (Farhangi et al., 2016). It is noteworthy that, thymoquinone, the main bioactive component of *N. sativa,* is also found in *Thymus vulgaris* (Taborsky et al., 2012) and *Origanum* (Ahmad et al., 2019) which also were suggested as potential therapeutic choices for hypothyroidism. Nonetheless, thymoquinone's poor bioavailability has limited this plant's clinical application.

Consequently, nanotechnology was suggested to overcome this problem and it has been utilized to treat various other diseases (Hannan et al., 2021). The main bioactive component, thymoquinone (TQ), was investigated using several nanoparticle formulations to test its potential against different diseases. For instance, oral administration of glycyrrhizin with polymeric nanoparticles in combination with TQ loaded into polymeric nanocapsules displayed a significant anti-hyperglycaemic effect. However, these nanoformulations when applied independently failed to display any encouraging pattern in the diabetes parameters being studied (Rani et al., 2019). Several other nanoparticles formulations have also demonstrated promising therapeutic benefits of TQ in the treatment of different cancers (Bhattasharya et al., 2020; Fathy, 2020; Nasri et al., 2020; Ramzy et al., 2020), as a wound-healing agent (Negi et al., 2020), as an anti-epilepsy agent (Ahmad et al., 2020) and to treat depression (Alam et al., 2020; Fahmy et al., 2020). Yet, none of those formulations was investigated against hypothyroidism. Hence, evaluating the effectiveness of nanoformulations in hypothyroidism experimental models is highly recommended.

4.2. Citrus paradisi and Citrus sinensis *(grapefruit and orange fruits)*

Citrus flavanones such as naringenin and hesperetin are the main active components in these plants. It has been reported that naringenin increased the serum thyroid-stimulating hormone (TSH) in old-aged rats, showing more potency compared with hesperetin within the pituitary-

thyroid axis. Nevertheless, both compounds maintained the capacity of the thyroid gland to produce thyroxine (T_4) which is reduced in old-aged rats (Miler et al., 2017).

The large hydrophobic ring structure of naringenin is the reason for its minimal bioavailability and low solubility. This problem has inquired the development of innovative naringenin nanoparticle strategies. oOne of these promising applications has used a simple nanoprecipitation procedure with a hydrophilic carrier, polyvinylpyrrolidone (PVP), enabling the usage of a lower dose of naringenin with improved bioavailability (Kumar and Abraham, 2016).

On the other hand, gold (Krishnan et al., 2017) and silver (Trendafilova et al., 2020) nanoparticles were also used to enhance the effect of hesperetin by solving the bioavailability problem related to the instability and low solubility, and were evaluated in many experimental models such as cancer (Ersoz et al., 2019), inflammation (Abdou and Elkader, 2021), and Alzheimer's disease (Babylon et al., 2021), while the thyroidal effect of these nanoparticle formulations remains to be investigated.

4.3. Costus pictus *(painted spiral ginger)*

Costus pictus, also known as insulin plant, fiery *Costus*, and spiral flag (Selvakumarasamy et al., 2021) is widely used in the traditional management of diabetes, and its methanolic extract has shown synergistic antidiabetic effect with metformin in the alloxan-induced diabetic model (Naik et al., 2022). The main active compounds in this plant are alpha and beta amyrin. Moreover, it has been revealed that *C. pictus* extract has potentially restored thyroid hormone levels in hypothyroidism rats induced by propylthiouracil. This animal model is usually associated with high rates of plasma total cholesterol. However, treatment with the plant leaf extract significantly reduced plasma levels of cholesterol as well as the inflammatory markers, blocked oxidative stress in the tissues, and inhibited renal and hepatic damage often observed in hypothyroidism. It is found that alpha and beta amyrins are the main active compounds thought to be responsible for the therapeutic effects (Ashwini et al., 2017). Interestingly, silver nanoparticles of *C. pictus* methanolic extracts have shown a surge in phenolic and flavonoid contents and increased antioxidant activity (Selvakumarasamy et al., 2021). Therefore, evaluating the nanoformulations on the hypothyroidism animal model is recommended.

4.4. *Withania somnifera (ashwagandha)*

The most active compounds in ashwagandha are withanolides, alkaloids, organic acids, and fatty acids (Abdel-Wahhab et al., 2019). It was revealed that the high contents of antioxidant compounds of ashwagandha methanolic extract significantly contributed to improving the tissue in propylthiouracil induced hypothyroidism, elevating the levels of thyroid hormones, and reducing oxidative stress. This was shown by a significant decrease in the serum levels of TSH levels and an increase in T_3, free T_3, and free T_4, as well as total T_4 hormones versus the untreated hypothyroidism rat group. In addition, the hypothyroidism rat group treated with ashwagandha extract exhibited lower serum concentrations of glucose and Il-6 and higher levels of blood haemoglobin, GPx, GSH, and Na^+/K^+-ATPase. However, this plant was also reported to have a beneficial effect on hyperthyroidism, which might indicate its modulatory effects on thyroid hormones (Abdel-Wahhab et al., 2019).

According to a recent promising study, nanoparticle-based technology was applied to achieve a higher efficacy of this plant against cancer by employing nanoparticles using an anti-mortalin antibody (MotAb) and folic acid (Wang, 2021). This might open the door for similar applications of nanoformulae to modulate thyroidal hormones.

4.5. Atractylodes macrocephala *(Bai zhu)*

The crude polysaccharides fraction and lactones fraction of *Atractylodes macrocephala* rhizome were found to be the most potent components of the plant. *A. macrocephala* rhizome was recommended for hypothyroidism treatment due to its effects in enhancing energy and substance metabolism, mostly by interacting with the signalling pathway of thyroid hormone, tricarboxylic acid (Krebs) cycle, glycolysis/gluconeogenesis, and fatty acid metabolism. Therefore, *A. macrocephala* rhizome directly affects thyroid hormone receptors A and B, increases the levels of T_3 and T_4, promotes glycolysis, and triggers the Krebs cycle to stimulate energy metabolism, as well as fatty acid metabolism in hypothyroidism rats as a suggested pathway for hypothyroidism treatment (Chen et al., 2021).

The effect of nanostructured particles lipid carriers of polysaccharides of *A. macrocephala* was investigated *in vitro* on bone marrow, showing a greater immunological stimulatory effect (Liu et al., 2018). However, to date, none have reported any findings concerning nanoformulations of this plant against thyroid hormone disorders.

4.6. Scutellaria baicalensis *(Chinese skullcap)*

Recently, *Scutellaria baicalensis* was proposed to suppress T_3, T_4, as well as the adrenergic activity in levothyroxine-induced hyperthyroid in animal models by increasing serum TSH, downregulating deiodinase-1, and upregulating thyroxine-binding globulin expression. This regulatory effect of thyroid hormone is thought to be responsible for *S. baicalensis* efficacy in the treatment of cardiovascular and anxiety disorders (Kim and Lee, 2019). Interestingly, *S. baicalensis* is one of the main herbs of Ahnjeonbaekho-tang (AJBHT) which is clinically reported as an effective medicinal plant in the treatment of Graves' disease (Kim et al., 2005) by controlling the expression of cyclic AMP. This anti-thyroid effect of AJBHT is attributed mainly to the compounds daidzein and baicalein which are considered the most active components.

On the other hand, zinc oxide nanoparticles have shown a potent scavenging activity (Chen et al., 2019). However, such a formulation against thyroid gland dysfunction is not discovered yet and should be explored.

4.7. Lycopus europaeus *and* Lycopus virginicus *(gypsywort and bugleweed)*

Lycopus europaeus extracts decreased thyroid gland weight, and reduced the TSH leading to a reduction in the levels of T_3 and T_4, in addition to increasing iodine absorption and storage and inhibiting the progress of goiter in animal models; with a blocking effect on adenylate cyclase, resulting in an inhibitory effect to the extreme thyroid stimulation. This extract has also reduced the luteinizing hormone levels. This confirms the central action nature of this plant. This effect is justified by the presence of rosmarinic acid as a major active compound (Al-Snai, 2019). On the other hand, *L. virginicus* extract has been recommended as a potent anti-thyroidal medicinal plant to control hyperthyroidism. It has been reported to have a remarkable inhibitory effect on the progress of Grave's disease, by reducing thyroid hormone and TSH levels. It also inhibited the conversion of T_4 in the target tissues (Kaplan and Dosiou, 2021). This effect is most probably due to the presence of phenolic compounds such as rosmarinic acid, chlorogenic acid, and luteolin-7β--glucuronide, which are the active constituents of this plant extract (Winterhoff et al., 1988). Also, a very recent noteworthy study has used rosmarinic acid in gold-based nano-formulation to treat anaplastic thyroidal carcinoma, showing promising results (Amaral et al., 2021).

4.8. Annona squamosa *(custard apple)*

The extract of *Annona squamosa* seeds has been highlighted for its likely therapeutic effects in managing hyperthyroidism in the animal model not only by reducing the serum levels of T_3 and T_4 and inhibiting the activity of both 5'-mono-deiodinase and hepatic G-6-Pase enzymes, but also by reducing the hepatic lipid peroxidation and improving the activities of superoxide dismutase as well as catalase. This indicates the safety and antiperoxidative efficacy of this plant, which is mostly related to the presence of the main active component, quercetin (Panda and Kar,

2007). However, to date, the nanoformulation of this plant extract was only investigated against cancer (Fadholly et al., 2020).

4.9. Salvia rosmarinus (rosemary)

It was reported by animal and *in vitro* studies that the aqueous extract of rosemary has a remarkable suppressive effect on the thyroid gland leading to lower secretion of T_4 and T_3 serum levels. This is due to the direct effect of rosmarinic acid which has the ability to block the immunoglobin effects on TSH receptors, decreasing the peripheral conversion of thyroid hormones, reversing the hyperplastic changes of the thyroid parenchyma, in addition to the anti-oxidative activity of this plant extract which is mostly attributed to phenolic diterpenes, carnosic acid and carnosol (Kasim et al., 2020). However, these phenolic compound molecules are highly susceptible to degradation by enzymatic activities, heat, light, oxidants, pH, and water. Hence, it was suggested that their stability should be maintained by being protected via encapsulation in silk fibroin nanoparticles before its application. This method has augmented the antioxidant activity of rosemary, owing to the efficacy of the encapsulation in stabilizing the phenolic compounds and improving their delivery (Hcini et al., 2021).

5. Conclusions

Endocrine disorders, especially diabetes mellitus, and thyroidal and hormonal imbalances, are gaining more scientific attention because of their critical complications and rising prevalence. Treatments of such ailments are mainly focused on the use of synthesised small molecules and hormone-replacement therapies which can manage or limit further impediments. The search for novel plant-derived treatments has been seen to have similar pharmacological effects, and sometimes better, besides the reduced cytotoxicity and adverse effects of the conventional treatments. Despite that, some extracts of medicinal plants or their isolated secondary metabolites were effective in preventing such diseases or impeding their progress. These medicinal plants are found to have numerous potential pharmacological effects by acting on diabetes mellitus type-1 and -2, insulin resistance, hyper and hypogonadism, polycystic ovarian syndrome, dysmenorrhea, male and female fertility, and hyper- or hypothyroidism. To our knowledge, not all the covered medicinal plants have been proceeded with *in vivo* or clinical studies. Thus, more scientific research is required to scrutinize the effects of these plants, plus, other species of the same genera, which might have similar or more potent activities. Moreover, we examined some nano-formulated extracts and isolated natural products which have been reported either for the discussed disorders or other types of diseases. Similarly, these nanoformulations require further studies on their targeted biological systems which in turn can lead to better future studies and prospects.

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Author contribution statement

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