IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A DRUG REVIEW OF PCOS WITH A FOCUS ON BIOLOGICAL AVTIVITY OF SOOTHAGAVAAYUKKU KIYAZHAM

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ABSTRACT

The *Siddha* system is one of the most conservative medical systems in the world. Awareness of traditional medicine is gradually increasing and people are benefiting more from natural treatments for their health problems. A traditional system of healing that originated in South India and is considered one of the oldest systems of medicine in India. This drug review aims to validate *siddha* herbal preparation *soothagavaayukku kiyazham* with scientific evidence. The medicinal uses and therapeutic effects of each ingredient used in this formula have been consistent with current research findings from various scientific publications. Based on the evidence of this Siddha literature and modern scientific studies, the keyhole is also presented, resulting in ovulation, anti-inflammatory, antioxidant, most of the ingredients of *Soothagavaayukku kiyazham* according to the review.

KEYWORDS

Soothagavaayukku kiyazham, PCOS, Siddha system, Drug review.

1.INTRODUCTION

Polycystic ovarian syndrome (PCOS) is one of the most common reproductive endocrine disorders with a broad spectrum of clinical manifestations. A polycystic ovary is an abnormally large numbers of developing egg seen to the ovarian periphery, looking like a ―String of pearls. Hallmark features of pcos include anovulation, hyperandrogenism, and polycystic ovaries. Other important manifestations of pcos include hypersecretion of luteinizing hormone, metabolic disorders, hyperinsulinemia, insulin resistance, glucose intolerance, dyslipidemia, hirsutism, acne, obesity, type 2 diabetes mellitus and infertility. Some long-term complications include cardiovascular events, endometrial cancer and psychological disorders such as stress and depression represent various symptoms associated with the disorder(1). Polycystic ovary syndrome (PCOS) is the most common hormonal disorder in women, with an incidence of 6-10% according to National Institutes of Health criteria(2). Soothagavaayukku kiyazham is a herbal formulation contains Three ingredients which is mentioned in Siddha Literature of *Urvasi rasavatha chitka vaithiya chitka pancharathinam*.Page number: 180. This drug use for *soothagavaayu* (pcos). The drug review of *soothagavaayukku kiyazham'* is a herbal formulation gives evidence for its therapeutic action mentioned in literatures. The ingredients of this drug are kollukavelai ver (*Tephrosia purpurea*),sukku (*zingiber officinale*) Athimadhuram *(Glycyrrhiza glabra*). This review describes the Description of the plant, chemical properties and pharmacological activities of each ingredient used in this formulation.

2.MATERIALS AND METHODS

Research design: Literature Review

Literature collected from

Siddha Literature: *Urvasi rasavatha chitka vaithiya chitka pancharathinam.*

Page number: 180

Publisher: R.C.Mohan

Published by: Thamarai noolagam

Year of Publication: 1993

Data collection:

Literature searching in electronic databases such as Science Direct, Pub Med, Pub Med

Cochrane and Google-Scholar for publications.

INGREDIENTS OF DRUG

- Kollukavelai ver (*Tephrosia purpurea*) -2 palam (70gm)
- Sukku (*Zingiber officinale*) -1/4 palam (8.75gm)
- Athimadhuram (*Glycyrrhiza glabra*) -1/4 palam (8.75gm)

DRUG PREPARATION

All the drugs will be authenticated by the Gunapadam experts and Botanist.All the purified ingredients will be pounded in iron mortar to a coarse powder.The coarse powder will be stored in an airtight container.The prepared kudineer chooranam will be added with 650ml (arai padi) of water and heated with low flame till the water condensed to 168ml (aazhaakku).

Drug name: Soothagavaayukku kiyazham

Dosage: Aazhaakku(168ml)

Route: oral

Indication: Soothagavaayu(pcos)

3.DRUG REVIEW

3.1 SUKKU (*ZINGIBER OFFICINALE*)

Fig: 1 Zingiber officinale

SCIENTIFIC CLASSIFICATION

- Kingdom - Plantae
- Division - Magnoliophyta
- Class - Liliopsida
- Order - Zingiberales
- Family - Zingiberaceae
- Genus - Zingiber
- Species - Z. officinale

DESCRIPTION

Zingiber is a species included in the Zingiberaceae family. This family includes up to 24 genera and about 300 species. The Zingiber family also includes about 20 species. The ginger plant has perennial tuberous or rhizome roots. The plant produces an upright annual stem (pseudo-stem), 60-90 cm high and dark green leaves. Its stems are covered with flat sheaths that can be detached from the stem; The stem has 8-12 leaves. The leaves are long-bladed or flat and sessile; are alternate (alternate), lanceolate late, linear late, spotted, 10-21 cm high and 2-2.5 cm wide. The wheelbarrow rises singly from the stem with a small stem. The removal of a ball is 12-30 cm; it is designed as a head surrounded by blades. The last grain is gradually separated. The ball is about the size of a thumb. Rhizomes are aromatic, thickly lobed, pale yellow, with simple alternate narrow oblong lanceolate leaves. Anthers are double, crown-shaped, thinly channel-like and horn-shaped[3]. Sukku originates from Southern China, from where it spread to the Spice Islands and other parts of Asia, and then to West Africa and the Caribbean[4]. The ovary is oval and three-celled, each containing many ovules and filamentous, funnel-shaped peripheral hairy stamens with horn-like stamens below the apex. This plant is widely cultivated throughout India, Bangladesh, Taiwan, Jamaica and Nigeria. This perennial plant grows in warm climates.

CHEMICAL CONSTITUTIONS

Z. officinale has been reported to contain essential oils, phenolic compounds, flavonoids, carbohydrates, proteins, alkaloids, glycosides, saponins, steroids, terpenoids, and tannins as major phytochemical groups[5]. Fresh extracts and dried extracts of Z. officinale are known to contain gingerols, 1,7-bis-(40-hydroxy-30-methoxyphenyl)-3,5-heptadione, adenine, 1-dehydro-3-dihydro-gingerdione,acetoxy-6-dihydroparadol, isogingerol, 5-methoxy-gingerol, methyldiacetoxy-gingerdiol, methyldiacetoxy-gingerdiol, 1-dehydro-gingerdiol, acetoxy-gingerol, shogaol, paradol, 1-(40-hydroxy-30-methoxy-ocytenyl-37-oxyphenyl) one, 1-(40-hydroxy-30-methoxyphenyl)-7-deken-3-one, 1-(40-hydroxy-30-methoxyphenyl)-7-dodecen-3-one, beta-sitosterol palmitate, isovaniline, glycol monopalmitate, hexacosanoic acid 2 ,3-dihydroxypropyl ester, maleimide-5-oxime, p-hydroxybenzaldehydeand 1-(omega ferulyloxyseratil)glycerol. Fresh ginger contains 80.9% moisture, 2.3% protein, 0.9% fat, 1.2% minerals, 2.4% fiber and 12.3% carbohydrates[6].

PHARMACOLOGICAL ACTIVITIES

ANTI-INFLAMMATORY EFFECTS

Ginger has long been used as an anti-inflammatory agent, and many of its constituents have been found to have anti-inflammatory properties. Ginger has been shown to share pharmacological properties with nonsteroidal anti-inflammatory drugs (NSAIDs) in that it inhibits prostaglandin synthesis by inhibiting cyclooxygenase-1 and cyclooxygenase-2. However, ginger can be distinguished from NSAIDs by its ability to inhibit leukotriene biosynthesis by inhibiting 5-lipoxygenase. His discovery preceded the discovery that dual inhibitors of cyclooxygenase and 5-lipoxygenase may have a better therapeutic profile and fewer side effects than NSAIDs. Zingiber officinale (and Alpina galanga) ginger extract (EV.EXT.77) was also found to inhibit the induction of several genes involved in the inflammatory response, including genes encoding cytokines, chemokines[7].

ANTI -CANCER ACTIVITY

The past 20 years, many researchers have identified the beneficial effects of ginger and its metabolites on various types and cell lines of lung, skin, prostate, liver, ovary, colon, breast, kidney, etc. Ethanol ginger extract applied topically to mouse skin showed a highly significant protective effect against skin tumour and was associated with inhibition of 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced epidermal ornithine decarboxylase, cyclooxygenase and cyclooxygenase induction. lipoxygenase activity[8]. Apoptosis-mediated cytotoxic or cytostatic effects were observed for [6]-gingerol and [6]-paradol in human promyelocytic leukemia HL-60 cells, as well as for four diarylheptanoids and two shogaols. Recent studies have shown that zingerone contains anticancer potential[9]. An important study reported that ginger root extracts and gingerol play an important role in inhibiting the growth of Helicobacter pylori CagA+ strains, which have a specific gene associated with the development of premalignant and malignant gastric lesions[10]. Previous findings described the potent antitumor activity of geraniol against various types of malignancies, including prostate, liver, ovarian, colon, and oral carcinomas[11]

ANTI-OBESITY ACTIVITY

Okamoto et al., 2011 reported that 6-GN inhibits weight accumulation and fat accumulation in mice.[12] A study by Tzeng and Liu (2013) showed that 6-GN inhibits rosiglitazone-induced adipogenesis by preventing oil accumulation and accumulation. enough reducing droplet size in 3T3-L1 cells[13]. Histochemical staining also allowed detection of oil droplets in fat cells in a concentration of 5-15 lg/ml. Decreased concentrations of fatty acid synthase and adipocyte-specific fatty acid binding protein have also been reported..

IMMUNOMODULATARY EFFECT

In a study by Zhou et al (2006) evaluating the immunomodulatory effects of ginger (Zingiber officinale Roscoe) oil, the volatile oil in ginger significantly inhibited T-lymphocyte proliferation and reduced total T-lymphocyte counts. It indicated that ginger essential oil affects both cell-mediated immune response and nonspecific proliferation of T lymphocytes and may have beneficial effects in several clinical conditions such as chronic inflammation and autoimmune diseases[14]

ANTI HYPERLIPIDEMIA

A recent study by Hapsari and Rahayuningsih (2014) showed the antihyperlipidemic effect of red ginger[15]. 34 female patients suffering from hyperlipidemia were given red ginger drinks at a dose of 3.2 ml/kg for 21 days. The results showed that subjects' low-density lipoprotein cholesterol (LDLC) decreased by 12% by the end of the treatment period. The antihyperlipidemic effect of red ginger extract is thought to be due to 6-gingerol, 6-shogaol and gingerdione, which are present in higher concentrations in red ginger than in other ginger varieties..

DYSMENORRHEA

Given the high prevalence of primary dysmenorrhea and its adverse consequences on quality of life, known drugs in dysmenorrhea [mephenamic acid and ibuprofen] and ginger have been studied in the medical students living at dormitories of universities. The results revealed that ginger capsule is effective in improving primary dysmenorrhea. However, determining the effects of ginger on the other symptoms associated with primary dysmenorrhea was recommended[16]. A recent research has shown the effect of powdered extract of ginger rhizome on primary dysmenorrhea experienced by nursing students at dormitories. The results showed that 500mg ginger three times in a day is appropriate to reduce pain of primary dysmenorrhea[17]. Another study found similar findings and suggested further studies to determine probable side effects and more accurate dosage in primary dysmenorrhea.

ANTIOXIDANT EFFECT

In rats, ginger reduces lipid peroxidation and restores the activity of superoxide dismutase and catalase, glutathione and glutathione reductase, and glutathione peroxidase glutathione-S-transferase [18]. In general, ginger experience (5%) shows less kidney damage due to oxidative stress induced by ischemia[19]. Phytochemical ginger contains free radicals generated in biological systems. Some free radicals are important for the production of energy in the oxidation process[20]. An increase in the production of free radicals indicates oxidative stress, which can cause DNA damage.

3.1 KOLLUKAVELAI VER (*TEPHROSIA PURPUREA*)

Fig:2 *Tephrosia purpurea*

Fig:3 *T.purpurea root*

SCIENTIFIC CLASSIFICATION

- Kingdom - Plantae (Plants)
- Division - Magnoliophyta
- Class – Magnoliopsida
- Order – Fabales
- Family – Fabaceae
- Genus – Tephrosia
- Species – purpurea

DESCRIPTION

Tephrosia purpurea is a small shrub-grows up to 1.5 meters tall. It has bipinnate leaves with 7-15 leaflets and the terminal leaf is single. The leaves are 10-32 mm long and 5-11 mm wide. Pea flowers are white to purple and arranged in inflorescences up to 25 cm long. Individual flowers have therioses 2-3 mm long. Lumps are straight and slightly curved upwards at the terminal end and can vary in length from 20-45mm and 3-5mm in width. After drying, the pods split open along two valves and reveal 2–9 black oblong seeds, 2.5–5 mm long and 1.8–3 mm wide[21,22]..

CHEMICAL CONSTITUENTS

The plant contains flavonoids such as rutin, purpurin, purpurenone and purpuritenin and quercetin, retenoids such as deguelin, eliptone, rotenone, tephrosine, and sterols such as sitosterol[23]. The presence of the isoflavone, 7,4-dihydroxy-3,5-dimethoxy-isoflavone and the chalcone (+)-tephropurpurin was also reported in Tephrosia purpurea. The most important components of TP are rutin, quercetin, the retenoids deguelin, eliton, rotenone, tephrosine, and lupeol[24,25], and minor components are the flavanones, lanceolatin A, B, and C, isoloncocarpin, and purpurin of the roots and whole plant. Pongamol[26,27]. isoflavone-7,4-dimethoxy-3,5-dimethoxy-isoflavone; chalcone (+)-tephropurpurin, (+)-purpurin, pongamoll, lanceolatino-B and pterocarpans.

PHARMACOLOGICAL ACTIVITIES

ANTIOXIDANT ACTIVITY

Ethanolic extract of TP possesses a definite prohealing action and improved collagen maturation by cross-linking and also increase in dry granuloma weight (Akkol et al., 2009). The ethanolic extract contains flavonoids which have potent antioxidant, antibacterial and free radical scavenging activities Chinniah et al., 2009). Antioxidants enzymes (Superoxide dismutase and Catalase) are known to quench the superoxide radial thus prevent the damage of cells caused by free radicals (Sinha et al., 1982), so that the scavenging effect might be one of the most important component of wound healing. The amount of total phenols which could be responsible for the anti oxidant activity of hydroalcoholic extract of Tephrosia purpurea[28]

ANTI-INFLAMMATORY ACTIVITY

T. purpurea plant extracts showed excellent anti-inflammatory activity, showing 58.2 and 68.4% inhibition, respectively. The inhibition percentage of the control was 50 and 72%, respectively. The production of superoxide ions is known to increase during inflammation and related processes. It may be possible that inhibition of superoxide generation in peritoneal macrophages is involved in the anti-inflammatory effects of T. purpurea[28]. β-Glucuronidase is found mainly in neutrophil lysosomes and plays an important role as a mediator in the initiation and progression of inflammation[29]. The formation of hydroperoxides (diene - conjugates) is one of the intermediate steps in membrane lipid peroxidation[30]. Lipid peroxidation leads to oxidative modifications of apoprotein, which are mainly involved in macrophage uptake and atherogenesis[31]..

IMMUNOMODULATORY ACTIVITY

To evaluate the effect of the flavonoid fraction on humoral response, its influence was tested on sheep erythrocyte-specific haemagglutination antibody titre in mice.It was found to significantly suppress the production of circulating antibodies.Whether its suppressive effect on the antibody responses was a direct result of its action on the B cells or an indirect effect via suppression of helper T cell functions is not known. The present study establishes the cellular and humoral immunomodulatory property of the flavonoid fraction of T. purpurea in vivo. Further studies are warranted to confirm these activities and explain its mechanism of action.[32]

ANTIBIOTIC ACTIVITY

Being secondary metabolites, the production of these antibiotic compounds by plants are affected by various stress conditions experienced by the plants. A decoction of T. purpurea is prescribed in traditional medicinal systems for the treatment of these conditions (Jayaweera,1982. The absence of antibiotic activity in the water extracts (which were boiled) of Tephrosia could be due to heat sensitivity of the antibiotic compound. Another possible reason may be that the compound is more soluble in alcohol than in water (due to higher polarity). From the results of the current study, it can be concluded that the ethanolic root extract of T.purpurea shows significant activity against Pseudomonas aeruginosa, two other Pseudomonas strains and two coliform strain. Ethanolic leaf extracts and water extracts of T.purpurea shows no activity against any of the isolates [33]

3.3 ATHIMADHURAM *(GLYCYRRHIZA GLABRA*)

Fig no:4 *Glycyrrhiza glabra*

SCIENTIFIC CLASSIFICATION

- Kingdom - Plantae
- Division - Angiospermae
- Class – Dicotyledoneae
- Order – Rosales
- Family – Leguminosae
- Genus – Glycyrrhiza

❖ Species – glabra Linn

DESCRIPTION

Glycyrrhiza glabra is a Greek name derived from two words glykys meaning sweet and rrhiza meaning root. Glabra, means smooth, refers to the fruits of this species, which are smooth (Akhundzadeh, 2000). Licorice is a perennial plant of the family Astragaleae and the subfamilies Fabaceae and Faboideae..Height of this plant is different and reaches to 100-200 cm. The plant has mass and excessive leaves. The leaves are alternatively attached to the stem and have 4-7 leaflets and a terminal leaflet. Leaflets are dark green. Flowers are seen irregular and crowded on terminal spikes in yellow, violet or purple colors. Length of flowers reaches to more than 1 cm. Plant flowers late spring and early summer (June-July). Fruit is an oblong pod, 2-3cm long and brown in color. Sides of fruit are thin and become less or more peaked. There are 3-5 brown seeds inside the fru that are like bean. Seed layer is thick and weight of one thousand seeds is about 10 gram. Length of root is different between 30-60 cm depending on species of plant and climatic condition of growing place. Length of root in dry regions and light soils reaches to 200 cm. Root and rhizome have medicinal uses. Glycyrrhiza glabra grows in deep valleys with full sun mostly in well-drained soils[34].

CHEMICAL CONSTITUENTS

Glycyrrhiza glabra L. roots contain several active compounds, including flavonoids, such as liquirtin, rhamnoliquirilin, liquiritigenin, prenyllicoflavone A, glucoliquiritin apioside, shinpterocarpin, licopyranocoumarin, glisoflavone, licoarylcoumarin, coumarin-GU-12, and saponins, namely, glycyrrhizin (60-times more sugary than sugarcane). Glycyrrhizin, a saponin compound, as well as its aglycone glycyrrhetinic acid, are the potent components in *G. glabra*. Glycyrrhizin consists of glycyrrhetic acid and triterpenoid aglycone, associated with glucuronic acid disaccharide, and it can be found naturally as calcium and potassium salts in licorice root [35,36]. In humans, glycyrrhizin can be metabolized and converted to glycyrrhetinic acid and, thus, the pharmacological activities of glycyrrhizin are similar to those of glycyrrhetinic acid[37].Raw and tea licorice infusions contains protein, fat, moisture, raw ash, fiber, silica, carbohydrates, minerals (calcium, phosphorus, sodium, potassium, zinc, and copper), and amino acids[38].

PHARMACOLOGICAL ACTIVITY

HORMONAL ACTIVITY

Licorice can affect cortisol and estrogen activity and reduce testosterone synthesis[39]. Glycyrrhiza contains glycyrrhizin and 18-β-glycyrrhetinic acid, which have mineralocorticoid properties and thus may inhibit cortisol metabolism. Licorice can reduce the side effects of the diuretic effects of spironolactone in patients with polycystic ovary syndrome (PCOS)[40]. Decreased levels of 11-β-HSD can lead to higher cortisol levels in humans, which ultimately interact with mineralocorticoid receptors and promote sodium ion reabsorption. Licorice can inhibit 3-β-hydroxysteroid dehydrogenase, 17-β-hydroxysteroid dehydrogenase and 17,20-lyase enzymes, which are mainly involved in the metabolism and thus synthesis of androgens and estrogens [41]. Licorice extracts reduce the activity of the enzyme 11-β-HSD, which catalyzes androgenic steroids into the testosterone hormone, thus lowering serum testosterone hormone levels[42]. 25 mg Glycyrrhiza glabra alcoholic extract can exert a strong estrogenic effect through uterine retention and vaginal opening. Glycyrrhiza isoflavones can affect sexual development, weaken the estrous cycle and alter the function of the ovaries, hypothalamus and pituitary gland. For this purpose, glabridin is used to treat menopausal symptoms and has a similar effect to that of 17-β-estradiol. It has also been found that isoliquirite and formononet can stimulate spermatozoa during fertilization .

ANTI-OBESITY AND HYPOLIPIDEMIC EFFECT

Acetyl CoA dehydrogenase and acetyl CoA carboxylase are two very important enzymes involved in lipid metabolism[43]. Glycyrrhiza glabra increased the earlier level and decreased later and then played a crucial role in the fight against obesity. In a laboratory experiment, ethanol extract of glabridin, ethyl acetate-soluble, water-soluble, and hexane-soluble fractions of Glycyrrhiza glabra lowered serum total cholesterol, triglycerides and increased serum HDL (High Density Lipoprotein)[44].

EFFECT ON FERTILIZATION

Aqueous extract of licorice increases the rate of in vitro fertilization (IVF)[45]. Artificial insemination is an assisted reproductive technique in which pregnancy can be achieved artificially by inserting sperm into the female reproductive organs. Artificial insemination is crucial in breeding and in the treatment of human infertility[46]. In this process, after a certain period of time, the released sperm undergoes a maturation process, then causes the acrosome reaction and finally the egg is fertilized. Two aqueous licorice extracts, isoliquiritigenin and formononetin, have been found to improve IVF rates in a rodent model. Estrogen affects sperm activation and acrosome reactions. Isoliqueiritigenin has a strong estrogen-like effect. Formononetin contributes to sexual development, including the timing of puberty, ovarian function, impairment of the estrous cycle, and pituitary and hypothalamic function. Isoliquiritigen and formononet affect sperm during fertilization, but do not affect embryos..

ANTI-DEPRESSANT ACTIVITY

Glycyrrhizin, a component of aqueous Glycyrrhiza root extract, has shown antidepressant activity in mice using the forced swim test (FST) and tail suspension test (TST). The extracts were administered orally for 7 consecutive days to male mice at doses of 75, 150 and 300 mg/kg in separate groups. For both FST and TST, a dose of 150 mg/kg showed reduced immobility time without impairing locomotor activity[47].

ANTI CANCER EFFECT

The cytotoxic activity of the methanol extract of Glycyrrhiza was tested by shrimp mortality bioassay methods in salt water. The extract exhibited potent cytotoxic activity with an LC50 value of 0.771 µg/ml[48]. Isoliquiritigenin isolated from the roots of Glycyrrhiza glabra inhibited 1,2-dimethylhydrazine-induced colon and lung tumors in mice when administered at a dose of 300 mg/kg[49]. The cytotoxic activity of different extracts of the bacterium Glycyrrhiza glabra was tested on a transformed cell line in mice. The effect of ethanol extract of Glycyrrhiza glabra extract (50, 100, 150 and 200 µg/ml) on HSP90 expression, growth and apoptosis in HT-29 colon cancer cell line was investigated. The decrease in cytokine VEGF levels and microvessel density in the peritoneum of mice treated with Glycyrrhiza glabra indicated that the plant extract reduced VEGF production.[50]

4.RESULT AND CONCLUSION

Through this extensive review on recent research reports maximum scientific validation has been carried out on various pharmacological actions and therapeutic benefits of each ingredient of *Soothagavaayukku kiyazham.* The ingredients present in this formulation have effective in the treatment of *Soothagavaayu* (PCOS). Based on evidence from this Siddha literature and modern scientific studies, a keyhole has also been presented, resulting in antioxidant, anti-inflammatory, anti-cancer and hormonal activity, which is the most abundant ingredient in Soothagavaayukku kiyazham, as shown in this review. Thus, additional scientific publications on preclinical and clinical evaluation are the need of the hour to gain wide acceptance among the public and the scientific community.

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