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A Systematic Review on the Effects of *Jīwanīya Ghana Kashaya* in the Management of Reduced Progesterone in Spontaneous Abortion

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Abstract

Progesterone plays a crucial role in supporting pregnancy through a variety of endocrinological and immunomodulatory functions. It promotes vascular growth in the endometrium, supports nutrient secretion for embryo development, and prepares the uterine lining for implantation. Progesterone's immunomodulatory properties are vital for preventing immune rejection of the fetus, as it suppresses the activation of immune cells and cytokine production, maintaining a suitable immune environment for pregnancy. A systematic literature review was conducted in this study about the herbal plants used in the preparation of *Jīwanīya Ghana Kashaya* and their pharmacological effects by using recent evidence published in the PUBMED Central database from 2000 to 2023. The PRISMA model was applied in selecting the relevant publications. The herbs in *Jīwanīya Ghana Kashaya*, exhibit diverse pharmacological activities that could aid in preventing miscarriage. These herbs display anti-inflammatory, antioxidant, and immunomodulatory effects by modulating key cytokines and signalling pathways involved in immune responses. For instance, *Leptadenia reticulata* inhibits prostaglandins and reduces inflammation by regulating cytokines like IL-2 and TNF-α. *Withania somnifera* suppresses NF-kB activity and reduces NO production, while *Asparagus racemosus* boosts antioxidant enzymes and modulates the immune system. *Pueraria tuberosa* and *Glycyrrhiza glabra* further reduce inflammation and oxidative stress by inhibiting pro-inflammatory cytokines and enhancing antioxidant activity. Notably, *Jīwanīya Ghana Kashaya* may target multiple signalling pathways like TNF, TLR4, and MAPK, contributing to its potential in mitigating the effects of spontaneous abortion. These findings highlight the therapeutic potential of these herbs in managing pregnancy- related complications such as spontaneous abortion.

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Keywords: Immunomodulator, *Jīwanīya Ghana Kashaya*, progesterone, spontaneous abortion

Introduction

Jīwanīya Ghana Kashaya is one of the decoctions named as *Panchashath Mahakashaya* mentioned in *Caraka Samhita* (Shirke, 2022) [1]. *Jīwanīya ghana* has properties like *garbhasandhankrita* (retention of fetus), *stanyakrita* (promotes lactation), *vrimhana* (nourishment), *vrishya* (aphrodisiac), *snigdha* (unctuousness), and *sheeta* (cold potency) (Rupareliya, Donga and Gandhi, 2021) [2]. The decoction of *jīwanīya ghana* is comprised of ten herbal medicines such as *jiwanthi* (*Leptadenia reticulata*), *kakoli* (*Roscoea procera*), *kshirakakoli* (*Lilium polyphyllum*), *medha* (*Polygonatum verticillatum*), *mahamedha* (*Polygonatum cirrhifolium*), *mudgaparni* (*Phaseolus trilobus*), *mashaparni* (*Teramnus labialis*), *jiwaka* (*Malaxis acuminate*), *rishabhaka* (*Microstylis muscifera*), *madhuka* (*Glycyrrhiza glabra*) (Tadvi, Dorkhande and Paradkar, 2018) [3].

From these ten herbs *Roscoea procera*, *Lilium polyphyllum*, *Polygonatum verticillatum*, *Polygonatum cirrhifolium*, *Malaxis acuminate* and *Microstylis muscifera* are herbal plants which are growing in the region of Himalaya, India. To collect the original herbs from Himalayan habitat is a difficult task and also these plants are listed as endangered (Tadvi, Dorkhande and Paradkar, 2018 [3]; Ahana and Hegde, 2018 [4]). The Government of India has implemented policies to safeguard and promote the conservation, cultivation, and sustainable extraction of rare and endangered medicinal plants. However, despite these efforts, there are six rare herbs that are crucial ingredients in the "original" ancient recipe for *jīwanīya ghana* named as *kakoli* (*Roscoea procera*), *kshirakakoli* (*Lilium polyphyllum*), *medha* (*Polygonatum verticillatum*), *mahamedha* (Polygonatum cirrhifolium), jiwaka (Malaxis acuminate) and rishabhaka (*Microstylis muscifera*) but are now missing from commercial formulations. Instead, substitute herbs are being used. The non-availability of authentic plants, confusion in vernacular names, and lack of chemical-markers have contributed to the substitution or adulteration of these plants. Unfortunately, these herbs, which are on the brink of extinction, are listed as critically endangered or endangered species. This highlights the urgent need for their preservation and proper identification to prevent further loss and ensure the authenticity of traditional medicine formulations (Sharma *et al*., 2019) [5]. Therefore, substitutes are used in the present formula which are already prescribed by *Bhavaprakasha Nighantu* as follows (Tadvi, Dorkhande and Paradkar, 2018[3]; Gholap and Pedhekar, 2019[6]).

Table 1: Substitutes used in the current formula of *Jīwanīya Ghana Kashaya* (Tadvi, Dorkhande and Paradkar, 2018 [3]; Gholap and Pedhekar, 2019 [6]

Herbal plant	Botanical name	Substitute	Botanical name
Kakoli	Roscoea procera	Ashwagandha	Withania somnifera
Kshirakakoli	Lilium polyphyllum		
Medha	Polygonatum verticillatum	Shatavari	Asparagus racemosus
Mahamedha	Polygonatum cirrhifolium		
Jiwaka	Malaxis acuminate	Vidari	Pueraria tuberosa
Rishabhaka	Microstylis muscifera		

As several medicines in this *kashaya* preparation are rare to find, substitutes are considered instead of those herbs. Then the proposed *Jīwanīya ghana kashaya* utilized in the present study will be of total 7 herbal medicines; *jiwanthi* (*Leptadenia reticulata*), *ashwagandha* (*Withania somnifera* Dunal.), *shatavari* (*Asparagus racemosus* Willd.), *mudgaparni* (*Phaseolus trilobus*), *mashaparni* (*Teramnus labialis*), *vidari* (*Pueraria tuberosa* DC.) and *madhuka* (*Glycyrrhiza glabra*).

The primary complication frequently encountered in pregnancy is early pregnancy loss, commonly referred to as spontaneous abortion. Spontaneous abortion is defined as a pregnancy loss occurring repeatedly for three or more times, transpiring before 18-28 weeks of gestation (Ford and Schust, 2009 [7], Hu *et al*., 2018 [8]). According to the International Classification of Diseases (ICD), it is characterised as the non-induced death of an embryo or fetus or the expulsion of products of conception prior to 22 weeks of gestation or weighing less than 500 grams (WHO, 2022 [9]).

Progesterone, a key female sex hormone primarily produced by the corpus luteum, plays a vital role in pregnancy (Haas, Hathaway and Ramsey, 2018) [10]. It facilitates the transition of the endometrium from the proliferative phase to the secretory phase, creating a favorable environment for embryo attachment and development in the uterus. Maintaining optimal progesterone levels (15-20 nmol/L in the early luteal phase and 35-50 nmol/L in the middle luteal phase) is crucial for successful pregnancy (Nagy *et al*., 2021) [11]. Progesterone not only prepares the endometrium for implantation but also helps maintain the gestational sac inside the uterus and harmonizes the body's immune system.

After ovulation, the corpus luteum synthesizes progesterone, which continues in the early weeks of gestation. Eventually, around the 12th week of pregnancy, the placenta takes over progesterone production, replacing the corpus luteum as the primary source. Inadequate progesterone levels during the luteal phase of the menstrual cycle or early pregnancy are associated with an increased risk of miscarriage. Therefore, women with progesterone levels of 10ng/mL or lower in early pregnancy may receive daily supplementation of 100 mg progesterone until the 10th week. Additionally, women undergoing assisted reproductive technology (ART) may require progesterone supplementation during the luteal phase of their menstrual cycle to prepare the uterine lining for successful implantation (Lim, Cheng, and Wong, 2013) [12]. Progesterone's critical role in pregnancy highlights the importance of maintaining appropriate levels for healthy gestation and reducing the risk of complications.

From all the causes of spontaneous abortion, this study focuses on the endocrine intervention, primarily the association of Progesterone hormone. Currently for the cases with spontaneous abortion, progesterone supplementations are prescribed in early pregnancy via orally, vaginally or intramuscularly. But in spite of having benefits of progesterone supplementation in early pregnancy, there are records of increased risk of Hypospadias in infants and further studies have been recommended in this regard (Czyzyk *et al*., 2017) [13]. ART, which is a major concern with enormous potential to help with conceiving, is a complex procedure consisting of several steps if one of which is applied incorrectly would result in failure in the conception (Farquhar and Marjoribanks, 2018) [14]. It is also associated with adverse effects, such as ovarian hyperstimulation syndrome, cycle cancellation and multiple pregnancy with higher prevalence of birth defects (Farquhar and Marjoribanks, 2018 [14]; Orvieto *et al*., 2021 [15]). That means there are disputes regarding progesterone supplementation and ART therapy in early pregnancy as a preventive method of Spontaneous abortion and this could be identified as a breakthrough point for Ayurvedic medicine to intervene in this regard to discover more efficient, competent and conservative treatment to be introduced. The present study is to focus on how *Jīwanīya ghana kashaya* could be applied in managing Spontaneous abortion occurring by reduced Progesterone level in the proliferative phase (Day 21) or luteal phase of the menstrual cycle of a patient with such a history.

Methodology

A systematic literature review was conducted with the objective of updating the knowledge about the herbal plants used in the preparation of *Jīwanīya ghana kashaya* and their pharmacological effect by using recent evidence published in the PUBMED Central database. The literature survey was conducted during the period from January 2000 to June 2023. In this survey, the terms "*Leptadenia reticulata*" OR "*Jivanti*" AND "pharmacology", ("*Withania somnifera*" OR "*Ashwagandha*") AND "phytochemical", *Asparagus racemosus*, *Phaseolus trilobus*, *Teramnus labialis*, "*Pueraria tuberosa*" OR "*mashaparni*" AND pharmacology and "*Glycyrrhiza glabra*" were used as the keywords. The term “AND” and “OR” were used as the Boolean operators to identify the relevant publications. The PRISMA model was applied in selecting the relevant publications. The survey was limited to the recent 23 years and filtered using the keywords “Title” and “Abstract”.

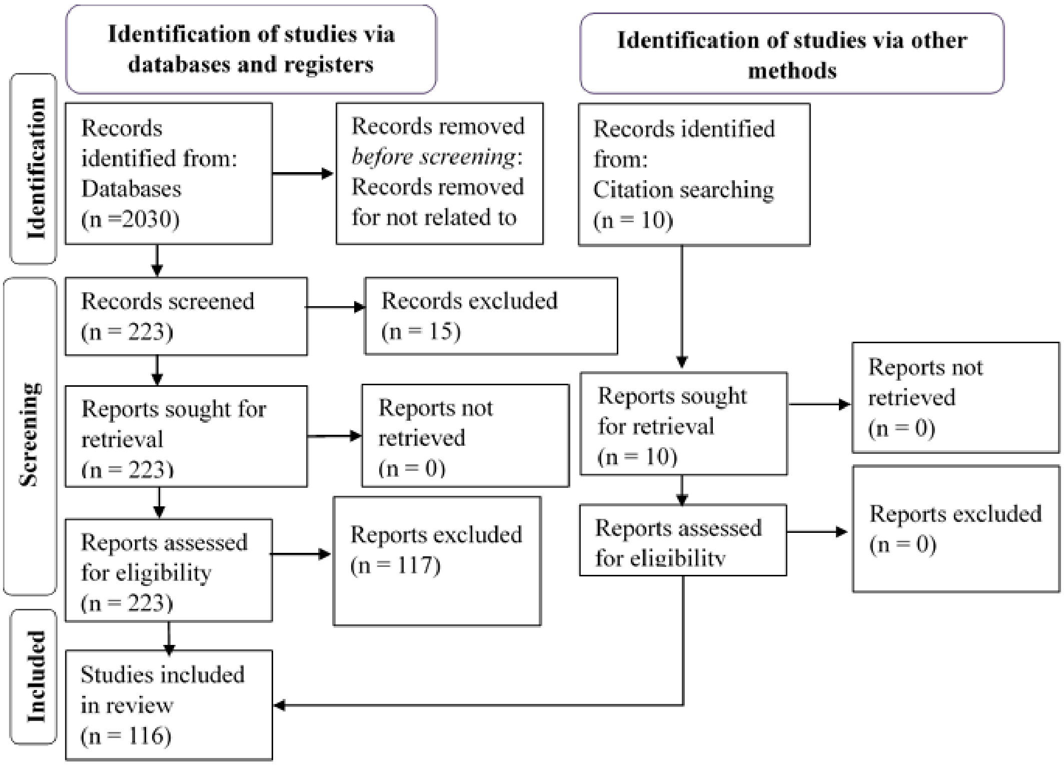

Chart 1: PRISMA flowchart of the systematic literature review

Only 44 studies were available by searching the key terms “*Leptadenia reticulata*” OR "*Jivanti*" AND "pharmacology" in PubMed Central database from 2000 to 2023. Of these, 10 studies were selected where the key terms are included in the content. Among them two were removed due to irrelevant data. Finally, eight studies were identified that specifically addressed the pharmacological effects and phytochemicals of *Leptadenia reticulata*. From 2000 to 2023, 1838 results were found by searching the key terms ("*Withania somnifera*" OR "*Ashwagandha*") AND "phytochemical" in PubMed Central database, but only 4 studies were available which were relevant with the title and 25 studies with the abstract. Among them only 15 studies were identified that specifically addressed the pharmacological effects and phytochemicals of *Withania somnifera*. 928 results were found by searching the key term “*Asparagus racemosus*” in PubMed Central database, but only 25 studies were available which were relevant with the title. Among them only 11 studies were identified that specifically addressed the pharmacological effects and phytochemicals of *Asparagus racemosus*. 30 results were found by searching the key term “*Phaseolus trilobus*” in PubMed Central database. No filters used and no titles found with the plant scientific name. Only 5 studies were available which were identified that addressed the pharmacological effects and phytochemicals of *Phaseolus trilobus*. 48 results were found by searching the key term “*Teramnus labialis*” in PubMed Central database. Only 7 studies were available which were identified that addressed the pharmacological effects and phytochemicals of *Teramnus labialis*. 30 results were found by searching the key terms "*Pueraria tuberosa*" OR "*mashaparni*" AND pharmacology” in PubMed Central database. 129 studies were found but 20 studies were selected which were identified that addressed the pharmacological effects and phytochemicals of *Pueraria tuberosa*. After screening only 12 studies were relevant with the present study. 30 results were found by searching the key terms “*Glycyrrhiza glabra*” in PubMed Central database. 4834 studies were found and among them 148 studies were selected by filtering with the title. 139 studies were selected which were identified that addressed the pharmacological effects and phytochemicals of *Glycyrrhiza glabra*. After screening only 39 studies were selected for the literature review purpose.

Results

Leptadenia reticulata

Phytochemical properties of *Leptadenia reticulata* found in the literature survey was mainly α & β amyrin, ferulic acid, luteolin, diosmetin, rutin, β-sitosterol, stigmasterol, hentriacontanol, simiarenol, apigenin, reticulin, deniculatin, leptaculatin, lupanol 3-O diglucoside, leptidine 1, luteolin, triterpenoids, leptadenol, n-tricontane, cetyl alcohol, β-sitosterol, β-amyrin acetate, diosmetin, and l-α-tocopherol in the whole plant (Mohanty *et al*., 2017 [16], Nema, Agarwal and Kashaw, 2011 [17], Sharma *et al*., 2019 [18]). The pharmacological effects of Leptadenia reticulata were anti abortifacient action of root by inhibition of PGF2 alpha by reducing the levels of prostaglandins, antioxidant effect by scavenging diphenylpicrylhydrazyl (DPPH), hydroxyl, and nitric oxide radicals, hydrogen peroxide scavenging and $FeCl_3$ reducing and increase in the activity of antioxidant enzymes, superoxide dismutase (SOD), and catalase (CAT), anti-inflammatory activity by reducing the levels of pro-inflammatory cytokines IL-2, IL-6, and TNF-α, immunomodulatory activity by and reducing glutathione, SOD, and CAT activities along with protective effects against immunosuppression induced by chromate (VI) (Mohanty *et al*., 2017 [16], Islam, Sun, and Zhang, 2021 [19]). Possesses hepatoprotective action through free radical scavenging properties and inhibits lipid peroxidation in CCl_4-induced hepatotoxicity (Nema, Agarwal and Kashaw, 2011) [17]. Also exhibits adaptogenic activity (Vyas *et al*., 2010) [20], galactogogue activity (Ravishankar and Shukla, 2007 [21], Vaidya and Devasagayam, 2007 [22]), vasodilator and anabolic effects (Vaidya and Devasagayam, 2007) [22].

Withania somnifera

Phytochemical properties of *Withania somnifera* were found as Withanine, somniferine, somnine, somniferinine, withananine, psuedo-withanine, tropine, psuedotropine, 3-α-gloyloxytropane, choline, cuscohygrine, isopelletierine, anaferine and anahydrine. Two acyl steryl glucoside viz. sitoindoside VII and sitoindoside VIII, two glycowithanoloids viz. sitoindoside IX or sitoindoside X (Vaishnavi *et al*., 2012) [23], Withanamides, withanolides (Withaferin A and withanone), withanosides, withanolide glycosides, steroidal saponins, and lignanamides (Srivastava, Ahmad and Khan, 2015) [24], Withanosides I-XI, Withanone and withaferin A, withasilolides A-F and withasomniferol D, withaninsams A and B (Ha *et al*., 2022) [25]. The main related pharmacological effects of Withania somnifera were antioxidant activity by ABTS radical scavenging activity (Ha *et al*., 2022) [25], anti-inflammatory activity by inhibition of transcriptional iNOS protein expression and inhibitory effects on nitric oxide (NO) production in lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages (Baek *et al*., 2019) [26], increase progesterone level by excitatory effect on luteal cells via inhibition of oxidative stress (Nasimi *et al*., 2018) [27] and stimulation of the hypothalamus-hypophysis axis (Rahmati *et al*., 2016) [28], stress-relieving effect by moderating effect on the hypothalamus-pituitary-adrenal axis and reducing cortisol level (Lopresti *et al*., 2019) [29].

Asparagus racemosus

In *Asparagus racemosus* there was found 10 steroidal saponins (Shatavarins), racemofuran, alkaloids, proteins, starch, tannin, mucilage, steroids, phytosterols, carbohydrates, tannins, anthraquinones, saponins, glycosides, flavonoids, polyphenols, ascorbic acid in the root (Kongkaneramit *et al*., 2011) [30], saponins (shatavarins I-V), sarasasapogenin, steroidal saponins, immunoside, anthocynanin, cyanidin glycosides, phytoecdysteroids, glycoside-AR-4, asparagamine A, racemofuran, diosgenin (Gupta and Shaw, 2011) [31], Flavanoids, saponins, polyphenols, asparagamine a polycyclic alkaloid, racemosol a cyclic hydrocarbon (9,10-dihydrophenantherene), and polysaccharides (Jagannath *et al*., 2012) [32]. The pharmacological effects were observed as antioxidant activity and anti-apoptotic effect, phyto-estrogenic, anti-neurodegenerative, immune-adjuvant and antitussive effects by lipofectamine-induced apoptosis, increasing superoxide dismutase, catalase and ascorbic acid, decreasing lipid peroxidase product (malondialdehyde), inactivation of superoxide dismutase, amelioration of oxidative stress (Kongkaneramit *et al*., 2011) [30], inhibition of lipid peroxidation by elevation of antioxidant activity (Mitra, Prakash and Sundaram, (2012) [33], galactagogue effect by action of corticosteroids or an increase in prolactin, hormonal like effect (Gupta and Shaw, 2011) [31], anti-stess activity by inhibition of pro-inflammatory cytokines (interleukin 1β and tumour necrosis factor α), and production of nitric oxide. Antioxidant, neuroprotective and cholinergic effect by augmentation of cholinergic system due to its anti-cholinesterase activity, antidepressant activity by facilitatory effect on both serotonergic and adrenergic systems and augmentation of antioxidant defences (Alok *et al*., 2013) [34], immunomodulatory activity by inhibition of IL-6 expression (Pise, Rudra and Upadhyay, (2015) [35], anti-inflammatory activity and immunomodulatory activity by Inhibition of TNF-α (Plangsombat *et al*., 2016) [36], increase GnRh, FSH, LH, Estrogen, Progesteron by regulating the synthesis of luteinizing hormone by looped guanosine mono phosphate through as second messenger in pituitary, increase the number of corpus luteum cells, which consequently increases synthesis of progesterone hormone (Karimi *et al*., 2016) [37].

Phaseolus trilobus

Phaseolus trilobus presents with α- pinene, carvone, pulgeone, dalbergioidin, kievitone, phaseollidin, flavonoid glycosides viz quercetin, kaempferol, vitexin, and isovitexin as major phytochemicals in the whole plant (Sharma *et al*., 2019) [18], dalbergioidin, kievitone, phaseollidin and flavonoid glycosides viz. Quercitin, kaempferol, vitexin, isovitexin, friedelin, epifriedelin, stigmasterol and tannins in root, seed, leaves and sead coat, methionine, tryptophan and tyrosine in bean (Kaur, Sehrawat and Tripathi, 2012) [38]. It exhibits antioxidant activity by reducing the elevated levels of serum thiobarbituric acid reactive substance (TBARS) and elevate superoxide scavenging radical activity and reduced level of glutathione (Fursule and Patil, 2010) [39], central nervous system depressant and reduction in spontaneous motor activity by potentiating GABAergic inhibition in the CNS via membrane hyperpolarization leading to a decrease in the firing rate of critical neurons in the brain or direct activation of GABA receptor by the extracts (Kesha *et al*., 2015) [40], antioxidant activity by DPPH free radical scavenging activity, ferrous ion chelating activity, hydrogen peroxide radical scavenging activity, hydroxyl radical scavenging activity, deoxyribose degradation activity, β carotene bleaching activity, phosphomolybdenum reducing power, ferric reducing antioxidant power (Kolar *et al*., 2022) [41].

Teramnus labialis

Teramnus labialis occupies vitexin, bergenin, daidzin and 3-O-methyl-D- chiro –inositol as the major phytochemicals in aerial parts (Sridhar, Krishnaraju and Subbaraju, 2006) [42], fraxidin also in aerial parts (Fort *et al*., 2000) [43], flavonol glycoside ($C_{26}H_{28}O_{17}$) in the stem (Yadava and Jain, 2004) [44], fraxidin and galactomannan in the fruit (Chithra, Priya and Paul, 2019) [45]. It exhibits lactogenic activity by increasing serum prolactin, protein and glycogen content of mammary gland, and cortisol level (Sahoo, Bhaiji and Santani, 2016) [46], antioxidant activity by free radical scavenging in assays with the DPPH radical (Salimo *et al*., 2023) [47], antioxidant and lipid peroxidation effect by reducing the levels of tissues enzymatic antioxidant, non enzymetic antioxidant and enhanced the level of TBARS, increasing the levels of antioxidant enzymes (Superoxide dismutase, Catalase, Glutathione peroxidase, Glutathione reductase) and enhancing the level of non-enzymatic antioxidant Glutathione (Alagumanivasagam, Muthu and Manavalan, 2012) [48], anti-inflammatory activity by inhibition of 5-lipoxygenase pathway (Sridhar, Krishnaraju and Subbaraju, 2006) [42].

Pueraria tuberosa

Pueraria tuberosa consists of Puerarin, Daidzein, Genistin, Genistein, Lupinoside PA4, Tuberosin, 3-O-methylanhydrotuberosin, Puerarostan, β-sitosterol, Biochanin a, Biochanin B, Daidzin, Irisolidone, 4-Methoxypuerarin, Puerarone, Quercetin, Tectoridin, p-coumaric acid, Hydroxytuberosone, Puetuberosanol, Robinin, Tuberostan, Isoorientin, Mangiferin, Stigmasterol as major phytochemical compounds in the tuber and leaf (Bharti, Chopra, Raut, and Khatri, 2021) [49], Genistein, daidzein, stigmasterol, β-sitosterol, and stigmasta-3,5-dien-7-one in the tuber (Satpathy *et al*., 2021) [50], Puerarin, daidzein, biochanin-A and formononetin in tuber (Chauhan *et al*., 2013) [51]. It exhibits antioxidant effect by suppressing macrophage activation by inhibiting IκB, ERK, and p38 activity and reactive oxygen species production, activate AMPK and increase PTEN expression, inhibit LPS-induced NO production in a concentration-dependent manner, expression of iNOS proteins, stimulate catalase and total superoxide dismutase (CuZn- and Mn-SOD) activity, and mRNA and protein expression (Bharti, Chopra, Raut, and Khatri, 2021)[49], anti-inflammatory effect by reducing inflammatory regulators (TNF-α, IL-1β, COX2, and MMP-14) and inhibit HDAC1/HDAC3 signalling, reduce adipose tissue inflammation through the upregulation of PPARγ, which might result in alleviating insulin resistance in obesity, suppress the iNOS, COX-2, MyD88, and TLR-4 protein expressions and akt and ERK1/2 pathway activation, inhibit HMGB1 release by decreased HMGB1 acetylation via upregulating SIRT1 in a PPARδ-dependent manner, inhibition of COX-2 activity and decrease the expression of COX-2, TNF-α, IL-1β, iNOS, and 5- LOX, increase of anti-inflammatory cytokine (IL-10) Inhibit TLR4-NF-κB signalling pathway, suppress inflammatory cytokine and chemokine levels (TNF-α, IL-1β, IL-6, and MCP-1), (Bharti, Chopra, Raut, and Khatri, 2021 [49], Bulugonda *et al*., 2017 [52], Anilkumar *et al*., 2017[53]). Increase in DPPH and ferric radical scavenging activities (Kanthaliya *et al*., 2023) [54]. It has an androgenic effect by increasing the sexual behaviour and hormones level (FSH, LH and Testosterone by affecting on gonadotropin release hormone (GnRH)), activate hypothalamic pituitary gonadal axis (Chauhan *et al*., 2013) [51].

Glycyrrhiza glabra

The rhizome consists of Glabridin, Glycyrrhizin, 18-Betaglycyrrhetinic acid as the major phytochemical components (Sharma and Rathore, 2011) [55]. Licoagrodin, licoagrochalcones, licoagroaurone and licochalcone C, kanzonol Y, glyinflanin B and glycyrdione A was found by Franceschelli *et al*., (2011) [56]. Glycyrrhizin, glycyrrhetinic acid, liquiritin, liquiritigenin, glabridin, 18β-glycyrrhetinic acid in the root (Chowdhury, Bhattamisra, and Das, 2013) [57]. Liquirtin, rhamnoliquirilin, liquiritigenin, prenyllicoflavone A, glucoliquiritin apioside, 1-metho-xyphaseolin, shinpterocarpin, shinflavanone, licopyranocoumarin, glisoflavone, licoarylcoumarin, glycyrrhizin, isoangustone A, semilicoisoflavone B, licoriphenone, and 1-methoxyficifolinol, kanzonol R present in the root (El-Saber *et al*., 2020) [58]. It can attenuate the LPS-IFN-γ-induced inflammatory response by significantly decreasing the expression and activity of iNOS via NFκB, by influencing extracellular $O2^-$ production, and by modulating the antioxidant network activity of SOD, CAT and GPx (glutathione peroxidase) activity (Franceschelli *et al*., 2011) [56], exhibit scavenging DPPH free radicals, suppress the expression of pro-inflammatory genes via inhibition of NF-kB and PI3K activity and thus decrease the excessive generation of NO, PGE2, and ROS (Kaur *et al*., 2012) [59], influence the action of cortisol, reduce testosterone synthesis, and influence oestrogen activity, influence sexual development and impair oestrous cycling and ovarian and hypothalamus and pituitary glands function (Pastorino *et al*., 2018) [60], has antispasmodic and uterine relaxant effects, suppresses prostaglandin biosynthesis through inhibition of Cyclo-oxygenase and Lipo-oxygenase pathways reducing Leukotriene and Prostaglandin synthesis, has relaxant activity through voltage- dependent L-type Ca2+ channel blockade, can inhibit NO synthase and PGs synthesis (Jafari *et al*., 2019) [61], increase the maturation vaginal index and decrease the vaginal pH, has a positive effect on the growth of superficial cells of the vaginal mucus, decrease in lactobacilli lead to altered natural vaginal flora (Sadeghi *et al*., 2019) [62], inhibits phospholipase A2 activity resulting in inhibition of cyclooxygenase activity and prostaglandin formation that is a critical enzyme involved in numerous inflammatory processes, decrease the growth of endometrial implants, inhibit thrombin-induced platelet aggregation, has steroid-like anti-inflammatory effects similar to glucocorticoids, decreases cell proliferation, inhibits the expression of angiogenic and inflammatory proteins and induces cell cycle arrest or apoptosis, reduces macrophages number and tumor growth in the tumor microenvironment, suppresses the production of inflammatory cytokines, inhibits an isomer of platelet-activating factor and acetyltransferase resulting in an anti-inflammatory activity (Namavar *et al*., 2019) [63], improve ovarian morphology, oocyte maturation, and embryonic development, prevent vaginal atrophy, reduce vaginal dryness, soreness, itching, and dyspareunia, thickening of the theca layer, thinning of the granulosa layer of antral follicles, reduction of the number of the antral follicles, and induction of the number of follicular cysts, decrease LH/FSH ratio, has antagonistic properties on estrogen receptors (Tanideh *et al*., 2023) [64].

Discussion

Progesterone serves a diverse array of crucial endocrinological functions. It promotes the growth of blood vessels supplying the endometrium, encourages the endometrium to secrete nutrients vital for early embryo development, readies the uterine lining for embryo implantation, and sustains the endometrium throughout pregnancy. As gestation progresses, progesterone, through activation of progesterone receptor B, aids in mammary gland development and strengthens the pelvis in anticipation of labor. Moreover, pro-inflammatory cytokines like TNF-α and IFN-γ impede the growth of human trophoblast cells in vitro and induce apoptosis of human primary villous trophoblast cells, indicating their role in pregnancy complications such as recurrent spontaneous miscarriage (RSM). Given their cytotoxic and anti-pregnancy effects, the prevalence of Th1 or pro-inflammatory cytokines in RSM is unsurprising. Progesterone, renowned for its endocrinological significance in pregnancy, possesses intriguing immunomodulatory properties as well. It can suppress inflammatory reactions, immune cell activation, and cytokine production critical for immune responses. These capabilities are pivotal for pregnancy success, as maternal immune reactivity can disrupt pregnancy and lead to complications. Progesterone inhibits the activation of murine dendritic cells, macrophages, and natural killer (NK) cells. In rat dendritic cells stimulated with lipopolysaccharide (LPS), progesterone suppresses the production of pro-inflammatory cytokines like tumor necrosis factor (TNF)-α and interleukin (IL)-1β, along with Th1-inducing cytokine IL-12. Many of these inhibitory effects are mediated via NF-kB activation suppression. Additionally, progesterone curbs the production of chemokines such as macrophage inflammatory protein-1α, macrophage inflammatory protein-1β, and RANTES by CD8+ T lymphocytes (Raghupathy and Szekeres-Bartho, 2022) [65].

The pharmacological activities of the medicinal plants in *Jīwanīya ghana kashaya* encompass with valuable pharmacological activities which can induce serum progesterone levels which had been in a decreased level before.

Leptadenia reticulata can perform anti-abortifacient effect by inhibiting PGF2 alpha by reducing prostaglandin levels, antioxidant effects through scavenging various radicals and increasing antioxidant enzyme activity and anti-inflammatory activities by reducing pro-inflammatory cytokines and immunomodulatory effects against immunosuppression. *Withania somnifera* has antioxidant activity via radical scavenging pathways and anti-inflammatory effects by inhibiting iNOS protein expression and NO production, and suppressing NF-kappa B activation. *Asparagus racemosus* has antioxidant activity through radical scavenging and enzyme elevation and increase in milk yield, immuno-modulation, and anti-inflammatory effects. *Pueraria tuberosa* shows antioxidant effects by suppressing ROS production and increasing antioxidant enzyme levels and anti-inflammatory actions through inhibition of inflammatory proteins and pathways. *Glycyrrhiza glabra* shows anti-inflammatory activity via inhibition of NF-kB and pro-inflammatory gene expression and antioxidant effects by scavenging radicals and regulating antioxidant enzymes. Which means almost-all-of these plants exhibit a wide range of activities including antioxidant, anti-inflammatory, immunomodulatory, and anti-abortifacient effects, highlighting their potential therapeutic applications to increase the serum progesterone level.

In spontaneous abortion, the TNF-α, IL-10, TLR4, JUN, IL-1B, CYBB, PTGS2, APOE, SPI1, and MPO pathways might be targeted by the *Jīwanīya ghana kashaya*. Furthermore, C-type lectin receptor signaling pathway, chemokine signaling pathway, leukocyte transendothelial migration, TNF signaling pathway, MAPK signaling pathway, might correlate with the pharmacological activity of *Jīwanīya ghana kashaya*.

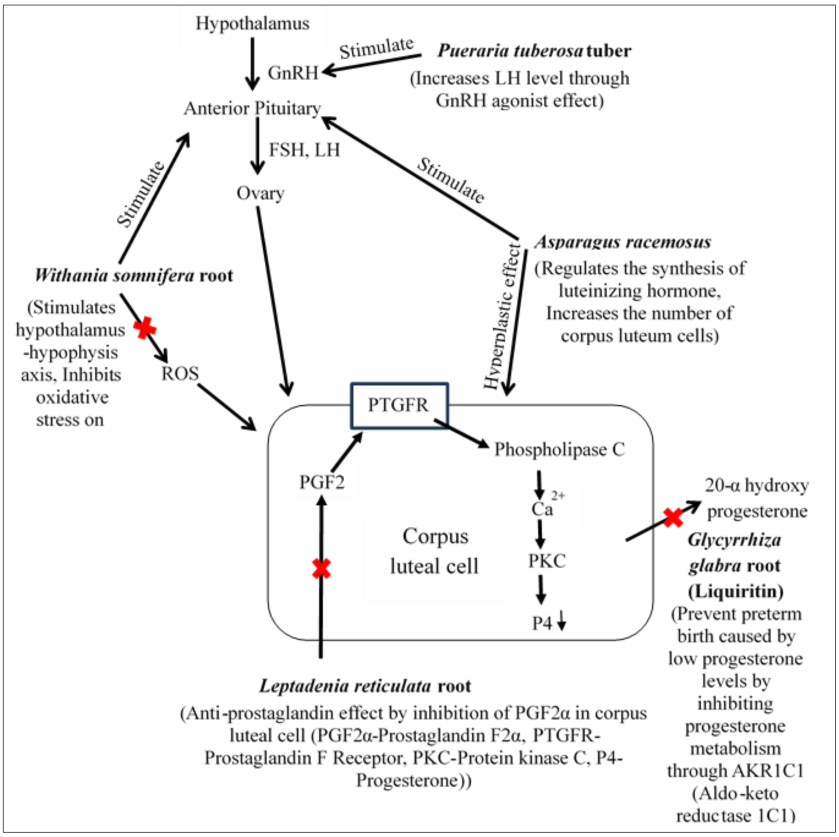

Fig 1: Phytochemical mechanisms of the herbs of *Jīwanīya Ghana Kashaya* to increase serum progesterone level

Conclusion

Through its pharmacological actions, *Jīwanīya ghana kashaya* exhibits abilities to modulate hormonal balance, enhance uterine receptivity, and regulate immune responses crucial for maintaining a healthy pregnancy. Furthermore, *Jīwanīya ghana kashaya* is known for its anti-inflammatory, immunomodulatory, and adaptogenic properties, which could mitigate the pro-inflammatory cytokine imbalance often associated with recurrent spontaneous miscarriage. These findings indicate that maternal immune effectors in generally, and cytokines in particularly, contribute to spontaneous abortion. Therefore, it can be hypothesised that the ingredients in *Jīwanīya ghana kashaya* demonstrate promising potential in preventing spontaneous abortion and are capable of preventing spontaneous abortion occurring by reduced progesterone level with the help of the pharmacological abilities of the drug to reduce the inflammatory reactions and inhibit the immune responses which are the properties that could effectively counteract factors contributing to spontaneous abortion.

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