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REVIEW ARTICLE

Putranjiva roxburghii Wall. and *Diplocyclos palmatus* (L.) C. Jeffrey as the potential sources of future drugs for infertility: a review

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Abstract

The changing lifestyle in recent years has greatly influenced the reproductive health of humans resulting in infertility-related problems, globally. One of the prominent approaches to address the infertility issue has been the use of plant-based safe and affordable drugs with no or minimal side effects. Two such medicinal plants, *Putranjiva roxburghii* Wall., (commonly called *putranjiva*) of the family Putranjivaceae and *Diplocyclos palmatus* (L.) C. Jeffrey (commonly called *shivlingi*) of the Cucurbitaceae family have been reported. There are reports stating the extensive use of these two medicinal plants by many countries especially India for their general and reproductive health benefits. The plants are an aid to azoospermia, aphrodisiac, menstrual disorder, semen disorders, infertility, diseases of female genital organs, oligospermia, conception, etc. These two plants act as a uterine tonic and help to enhance fertility when coadministered. As reported, the shivlingi is also believed to help conceive a male child when consumed by the female for 1-2 months on empty stomach. No doubt there are several reports stating the benefits of these two medicinal plants in various reproductive-related aspects but there is still a need for scientific work to be carried out to validate and justify the statements and claims made by practitioners or local communities as there are no or few studies being carried out in this area till date. No study shows work on the coadministration of these two medicinal plants. Therefore, extensive research in this field along with proper screening of phytosterols and other phytocompounds is still needed before the declaration and formulation of fertility drugs from these plants to provide hope to couples dealing with infertility-related issues.

Keywords: Reproduction; Infertility; Medicinal Plants; *Putranjiva roxburghii*; *Diplocyclos palmatus*

1. Introduction

Reproductive health, an essential component of the overall health of all animals, is the cornerstone of a healthy population. World Health Organization (WHO) addresses reproductive health as the reproductive processes, functions and systems at all stages of life. Reproductive inefficiency in either of the two partners halts the very process of giving birth to young ones. Thus, the fertility status of an individual becomes a predictor of future overall health (Cedars et al., 2017). The beginning of a new life is the culmination of a series of events finely tuned by endocrine signals, environmental, psychological, and lifestyle factors. Several reports and evidence highlight the critical determinants of healthy gametogenesis and embryonic development whose alteration results in poor fertility outcomes (Budhwar et al., 2017). The changing lifestyle in recent years has greatly influenced the reproductive health of humans leading to infertility issues globally. In the world of a fast-growing population, infertility occupies the epicenter of research work. Despite the advancement in medical science and Assisted Reproductive Technology (ART), some couples still struggle to conceive. Reproductive health in recent years is seen increasing interest and concern, with not all couples who desire a pregnancy turn out to be lucky. Thus, infertility has been recognized as a public health issue worldwide by the World Health Organization (WHO) (WHO, 2001; Boivin et al., 2007). Infertility to the World Health Organization (WHO, 2000), is the inability to conceive by sexually active, noncontracepting couple within a year. A healthy productive couple in their mid-twenties has only 20–25% chance of establishing pregnancy in each cycle (Shah et al., 2003). Infertility in humans is believed to affect 10-15% of couples with approximately equal likelihood contributed by both partners (Hayashi et al., 2012). The high rate of infertility and childlessness is one of the most critical and unappreciated reproductive health problems in developing countries (Bergstrom, 1992; Leke et al., 1993). Compared to other species, human being is highly inefficient in terms of reproduction. Their fertility rate per cycle is about 20%, and the accumulated pregnancy rate in couples with proven fertility is ~90% after 12 months and 94% after two years (Olmedo et al., 2000).

2. Reproduction and infertility

The endocrine hormone, namely follicle-stimulating hormone (FSH), plays a crucial role in the control of male and female reproduction. FSH is synthesized and secreted by the adenohypophysis, which binds to a plasma membrane receptor (follicle-stimulating hormone receptor, FSHR) that belongs to the G protein-coupled receptor (GPCR) superfamily. The FSHR exhibits a high degree of tissue specificity and is localized in Sertoli and granulosa cells of the testes and ovary, respectively (Simoni et al., 1997). FSH is required for average growth and maturation of ovarian follicles in women and normal spermatogenesis in men (Themmen and Huhtaniemi, 2000). Female mice with FSHb or FSHR gene knockout present an incomplete follicle development leading to infertility, whereas males display oligozoospermia and subfertility (Kumar et al., 1997; Dierich et al., 1998). Females expressing non-functional variants of the FSHR are infertile while males are oligozoospermic yet fertile (Aittomäki et al., 1995). To date only native forms of FSH either purified from urine or by using recombinant technology are used in reproductive medicine with no other pharmacological agents being currently available in clinics (Lunenfeld, 2004; Macklon et al., 2006; Croxtall and McKeage, 2011). Novel classes of FSHR agonists with varying pharmacological profiles can potentially help improve the overall efficiency of assisted reproductive technology.

The infertility problem is of a global focus to maintain healthy population growth with safe, affordable and effective family planning services. In almost 10-15% of the couples, it was observed that it's hard to detect the cause of infertility by routine diagnosis. Thus, infertility is regarded as a global health issue and is a multidimensional challenge with social, economic and cultural consequences and can take threatening proportions in countries with strong demographic problems, such as Greece (Roupa et al., 2009). A study in 2002 showed that about 2 million American women of reproductive age were infertile. Infertility is also common among men (Macaluso et al., 2010). In the U.S., it was observed that one in seven married couples suffered from fertility problems with abortion ranging approximately between 10–20% of clinically identified pregnancies. Out of live births, around 3% suffer from significant congenital disabilities, and 7% are born with low birth weight (Sheiner et al., 2003). The childless women are frequently stigmatized, neglected and isolated from the society, and they often fall prey to polygamy and domestic violence (Gerrits, 1997; Sundby, 1997; Papreen et al., 2000; van Balen and Gerrits, 2001; Richards, 2002; Inhorn and Balen, 2002; Araoye, 2003; Hollos, 2003; Wiersema et al., 2006).

It's a challenging task to check the fertility rate in a presumably fertile population due to its complexity and cost involved to conduct such studies. Fertility challenges may arise from many conditions caused by genetic abnormalities, infectious or environmental agents, delayed childbearing, behavior, and certain diseases (Macaluso et al., 2010). Infertility due to surgery or blockage, or due to abnormalities in the gametes, immunological and psychological factors also contribute to infertility related issues. Natural ageing processes, in addition, place a limit to human fertility. For many individuals, the fertility window closes prior to expecting. The causes of physiological state are further wide-ranging as diagnoses like ovulatory disorders, tubal unhealthiness, endometriosis, chromosomal abnormalities, gamete factors and unexplained sterility prevails. Infertility increased dramatically during recent decades; delayed timing of motherhood is one of the most important factors contributing to this problem which leads to poor oocyte quality and decreased ovarian reserves. In about 15% of male and 10% of impotent female subjects, genetic abnormalities may prevail. The most common 'cause' of sterility is solely 'unexplained', and this accounts for about two hundredths of couples (Uehara et al., 2001). Unexplained infertility is the case in which infertility studies show normal results. This problem occurs in about 15% of couples and is usually frustrating to both the physician and the couple as there is no existence of specific diagnosis. In couples with unexplained infertility, specific causes do exist but are unknown to date, or their detection is beyond the reach of the available diagnostic procedures (Crosignani et al., 1993).

There is often a coincidence of both male and female factors contributing to infertile couples. Also, it is found that the male partner contributes 45-50% of the infertility problem (Jungwirth et al., 2012). Reduced male fertility could be the result of congenital and acquired urogenital abnormalities, male accessory glands infections, varicocele (rise in scrotal temperature), genetic abnormalities, endocrine disturbances, and immunological factors. Out of 40–60% cases, the anomaly is of the semen analysis with no relevant history or abnormality on physical examination and endocrine laboratory testing (idiopathic male infertility). Semen analysis showed a decline in the number of spermatozoa (oligozoospermia), decreased motility (asthenozoospermia) and many abnormal forms on morphological examination (teratozoospermia). These male infertility abnormalities come together and are described as the OAT-syndrome (oligo-asthenoteratozoospermia) (Dohle et al., 2005). Spermatozoa are highly susceptible to damage induced by reactive oxygen species (ROS). This is caused due to the presence of a low concentration of scavenging enzymes within the cytoplasm and the presence of a high concentration of polyunsaturated fatty acids (PFA) within the plasma membranes (Jones et al., 1979; Ochsendorf and Fuchs, 1993; Aitken et al., 1994; de Lamirande et al., 1995; Sharma and Agarwal, 1996). High reductive oxygen species (ROS) levels are detected in 25-40% of the semen of infertile men and up to 96% of the semen of patients with spinal cord injury (Iwasaki and Gagnon, 1992; de Lamirande et al., 1995; Padron et al., 1997). Disorders in sperm production, epididymal maturation, sperm transport and accessory sex gland function are said to be the leading cause of male infertility. How to improve spermatogenesis has always been one of the most essential topics in male infertility research. Micronutrients especially vitamin A, vitamin C, vitamin E, zinc, and selenium, have been presently reported to be associated with spermatogenesis and androgen synthesis and secretion (Yu et al., 2014). There is little doubt that a man with a low level of semen parameters will be infertile and requires intra-cytoplasmic sperm injection (ICSI) if in need to reproduce. Likewise, it's not always mandatory that a man with better semen quality is able to produce offspring. Studies show that chance of conception increases with sperm concentrations of 40–60 × 106/ml and if the number of spermatozoa with normal morphology increase to 9–12% (Josso et al., 1998). Despite all the diagnostic difficulties, the WHO (1992) has suggested a diagnostic classification protocol for the male factor in infertile couples (Rowe et al., 1993). As per the data of Comhaire (1987) there is a considerable incidence of varicocele, as is idiopathic oligozoospermia.

Female infertility is a complex problem which is to be considered carefully in order to find effective interventions and solutions by the government and stakeholders. The causes of female infertility are problems in the fallopian tubes and the uterus, disorders of menstruation, sexual disorders, age and ovarian failure (Roupa et al., 2009). Factors such as female age, smoking, weight, diet, exercise, psychological stress, caffeine consumption, alcohol consumption and exposure to environmental pollutants affect reproductive performance (Homan et al., 2007). It has been studied that smoking in women significantly decreases the chance of conception (Hughes and Brennan, 1996; Augood et al., 1998). A significant increase in the incidence of unwanted infertility due to female reproductive ageing is observed due to societal changes in family planning (Weinstein et al., 1993; Abma et al., 1997; Ventura et al., 2001). After the age of 30, there is a decline in natural fertility that accelerates in the mid-30s and will lead to sterility at a mean age of 41 (Spira, 1988; Wood, 1989; Velde and Pearson, 2002).

Since the birth of Louise Brown in the United Kingdom, there has been high interest in the area of assisted reproductive technologies (ART) by scientists and the public. ART allows the manipulation of the fertilization process by scientists to overcome infertility problems. Yet there is limited treatment for infertility problem at present. Instead, various techniques of ARTs such as in vitro fertilization (IVF) techniques including ICSI and insemination is being used to circumvent infertility problems. In developed countries approximately 15% of the populations are believed to be affected by infertility leading to increase in the use of assisted

reproductive techniques resulting in a rise in prevalence of urogenital malformations, the incidence of testicular cancer and also decreased semen quality (Hakonsen et al., 2014). Though the practice of new knowledge in the field of medicine was made to daily practice by ART, there remains lacuna which is still to be filled (Kamel, 2013). A need for deeper understanding of the biology of reproductive organ development is mandatory (i.e., Testis and Ovary) to develop correct therapy for infertility issues.

The advancement and development in the field of molecular biology and genetics have a significant influence on the study of infertility in both females and males. These two disciplines are crucial for the diagnosis, assessment and research on infertility in the contemporary world (Olmedo et al., 2000). However, even with developed clinical means for diagnosis of reproductive deficiencies, about a fourth of clinical infertility issues are identified as idiopathic (Matzuk and Lamb, 2002). It was observed that the probability of live birth obtained through IVF treatment decreases after the age of 35 (Templeton et al., 1996) and the same is true for the implantation rate per embryo (van Kooij et al., 1996). The chance of not conceiving a first child within a year increased from 5% in women in their early 20s to approximately 30% or over in the age group of 35 years and older (Abma et al., 1997). In fact, female age has been considered as an essential interpreter of success in IVF treatment (Broekmans et al., 2006). The overall national success rate for all ART in the United States is 28%, varying by age group and diagnosis. The age of the woman, transferable embryo quality, ease of embryo transfer (ET), and endometrial receptivity are the significant factors that affect the outcome of in IVF. To improve IVF outcomes, numerous pharmacologic interventions have been studied as adjuvant therapy to enhance endometrial receptivity and to increase ovarian response to gonadotropin stimulation by improving follicle maturation, synchronizing the development of the follicular cohort, reducing cycle cancellation, preventing ovarian cyst formation and by eliminating unnecessary interventions (Bromer and Seli, 2008).

3. Plant-based medicines

Medicinal plants, an essential component of the ethnic medical system (Farnsworth, 1990) and a good source of secondary metabolites have long been used for drug synthesis and development (Parfitt, 1978). Medicinal plants play a central role in the development of human culture with their persistence as the "treatment of choice" for a multitude of health problems in populations throughout the world despite the increasing use of factory-made synthetic drugs (Leslie and Young, 1992; Phillips and Meilleur, 1998; Halberstein, 2005; Hassan, 2012). Traditional medicine (TM) has been utilized by many Latin American, African and Asian countries to meet some of their primary health care needs. About 80% of the world's population, especially in developing countries uses herbal medicine as their source of primary healthcare due to poverty or limited access to modern medicine (Farnsworth et al., 1985; Bisset and Wichtl, 1994; Mukherjee, 2002; Bodeker et al., 2005). Further, 1 out of 125 plant-based products ends up successfully as a drug (McCaleb, 1997) while the same is correct for only 1 in 10,000 out of synthetic chemicals (Farnsworth, 1994). It was studied that more than 80% of people in developing countries couldn't afford the most basic medical procedures, drugs, and vaccines. The complementary and alternative practices are more popular among the wealthier population in both developed and developing countries, although proof of their safety and effectiveness is modest.

Research in Ayurveda in recent years has been receiving more acceptance in India as well as abroad (Mashelkar, 2008; Joshi et al., 2011). Naranjo (1995) noted that over 20,000 medicinal plants were inventoried in by the World Health Organization (WHO), and 250 of these were analyzed to identify their biodynamic chemical components. At least 25% of the active compounds in currently prescribed synthetic drugs were first identified in plant sources (Balandrin et al., 1985); potential healing qualities and the investigation of their phytochemicals will gain the importance soon (Kendler, 1987; Youngkin and Israel, 1996; O'Hara et al., 1998; Meserole, 2001). Plants potentially act as a reservoir of useful chemical compounds which serve as drugs, provide newer leads and clues for modern drug design by synthesis (Varier, 1995; Evans, 2002). The medicinal properties of different plants are due to the presence of several valuable constituents such as saponins, tannins, alkaloids, alkenyl phenols, glycol-alkaloids, flavonoids, terpenes lactones, terpenoids and phorbol esters (Cox, 1990). Flavonoids are polyphenolic compounds present in diverse foods and beverages of plant origin, such as fruits, vegetables, soy products, tea and wine. They are most commonly known for the health benefits they provide against cancer and heart diseases, which are attributed to their antioxidant capacity (Ross and Kasum, 2002). Flavonoids are potent antioxidants inhibiting lipid peroxidation and platelet aggregation (Cirico and Omaye, 2006), protect the tissue from free radicals by direct scavenging reactive oxygen species (ROS), reactive nitrogen species (RNS) and activating antioxidant enzymes (Nijveldt et al., 2001). Nowadays, there is a growing interest in natural flavonoids for pharmacological uses in preclinical studies due to their beneficial health effects. Recently, substantial attention was paid to flavonoids as antioxidants and/or anxiolytic agents having superior pharmacological effectiveness (Zhang et al., 2004).

Particular botanical species containing chemical components that act as analgesics, anti-microbials, anti-inflammatories, immunostimulants, antidiarrheals, digestive aids, and fertility regulators are repeatedly consumed by a number of species of monkeys and apes (Glander, 1994; Baker, 1996; Plotkin, 2000). It is reported that for the management of similar diseases, injuries, and other health problems monkeys, gorillas, chimpanzees, and humans select some of the same plants (Huffman, 1997). The phenomenon of infertility has been prevailing throughout the world since the birth of the human race and may extend until the existence of the human race. Infertility affects around 8-12% couples worldwide, but the percentage may vary according to the region and country. The WHO has estimated the prevalence of overall primary infertility in India to be between 3.9 and 16.8%. In the event of infertility, couples tend to adopt traditional medicinal therapy such as Ayurveda, Siddha and Unani, which holds high esteem and trust in this field (Kumar, 2005). Moreover, the severe obsession with the modern medicinal system, due to adverse effects of synthetic drugs, has led people to adopt the traditional medicinal therapy like Ayurveda, Siddha and Unani. One of the prominent approaches to address infertility issue has been the use of plant-based safe and affordable drugs with no or minimal side effects. Herbal drugs play an essential role in health care programs, especially in developing countries (Shankar and Ved, 2003).

The Indian subcontinent is known for the diversity of forest products and age-old health care tradition. India is one of the mega biodiversity countries of the world, with only 2.4% of the land area but contributes 11% of the plant species (Kala et al., 2006). It is estimated that presently 25% of all drugs are plant-based, and many others are synthetically derived from compounds isolated from plants (Kala et al., 2006).

India is a massive depository of medicinal plants that are used in traditional medical practice to cure an uncountable number of ailments (Chopra et al., 1956). The popularity of herbal medicine is due to the toxicity and side effects of allopathic medicine, leading to an increase in herbal or plant-based drugs/medicines (Agarwal, 2005). The country has around 20,000 medicinal plant species recorded in scientific literature, out of which about 800 plant species have been used for curing different diseases by more than 500 traditional communities (Kamboj, 2000). India, one of the wealthiest countries in terms of forests and availability of medicinal plants, have depended upon the forests for religious beliefs, ornamentation, shelter, food, clothing, and most importantly for health care since time immemorial. Tribal dwellers in forest areas and hilly terrains mostly rely on these medicinal plants because of their effectiveness.

Tribal communities have a diverse knowledge of traditional medicines related to indigenous plants for basic healthcare needs (Tijani et al., 2008; Meenal et al., 2010; Saurabh and Kaushal, 2011). About 70 percent of the rural population of India depends on the traditional Ayurvedic system of medicine. The use of plants in the different Indian systems of medicine is recorded as:

Homeopathy 800, Tibetan 500, Modern 200, folk 4500, Ayurveda 2000, Siddha 1300 and Unani 1000. India is home to traditional and folk medicine practices with around 25,000 effective plant-based formulations being used. More than 1.5 million practitioners in India use the traditional medicinal system for health care. It is projected that more than 7800 industrial units are involved in the production of natural health products and conventional plant-based formulations are in India, which will need more than 2000 tons of raw material from medicinal plants annually (Pandey et al., 2008). As dietary supplements or ethnic traditional medicines, more than 1500 of herbals are sold (Patwardhan et al., 2005). At the rate of 20% annually, the market of ayurvedic drugs is estimated to expand. In India since the past ten years (1987-96) sales of medicinal plants in the world have grown by 25% showing the highest rate of growth (Masood, 1997). Throughout history, the use of herbs as medicine is the oldest form of healthcare practice known to humankind (Barnes et al., 2008).

However, the lack of documentation and rigorous quality control methods is a crucial obstacle, which has hindered the acceptance of alternative medicines in developed countries. There is an urgent need for documentation of traditional medications and research works associated with them (Dahanukar et al., 2000). An attempt for the standardization and consistency of the plant material to be used as the drug becomes extremely important with such backdrop. Through stepwise pharmacognostic and physicochemical studies, such standardization and consistency processes can be achieved. Appropriate identification and quality reassurance of the preparatory materials are mandatory to ensure reproducible quality of herbal medicines which contributes to their safety and efficacy. Simple pharmacognostic techniques used for the standardization of plant material include its morphological, anatomical and biochemical characteristics (WHO, 1998). There still remains a large percentage of traditional knowledge based on the use of various plant species with the indigenous people only; this fact is especially relevant for regions with hilly area or mountainous region which has less access or slow rate of development. Over one-third of the population still lack access to essential medicines in developing countries. The provision of safe and effective traditional medicine (TM) therapies could, thus, become a critical tool to increase access to health care (WHO, 2003). Hence there is an urgency to record and establish these traditional values at national and international levels as there is an increase in global interest and dependence on conventional knowledge. Consequently, research, education and training in this area have yet to gain due attention and support. The quality and quantity along with safety and efficacy data on traditional medicines are far from adequate to meet the standards needed to support their practice worldwide. Health care policies are one of the reasons for the lack of research data (WHO, 2000). Having recognized the significance of traditional medicine, greater attention is being paid by governments of many developing countries in recent years to promote the widespread application of the practice in health care. This has given a new impetus to relevant research, investment and design of programs in the conventional plant-based therapy in many countries (WHO, 2005).

4. *Putranjiva roxburghii* Wall. and *Diplocyclos palmatus* (L.) C. Jeffrey

Medicinal plants have been found recognized and utilized by primates for their healing properties. Two such vital medicinal plants i.e., *Putranjiva roxburghii* and *Diplocyclos palmatus*, with several health benefits and endowed with various classes of phytochemicals in them have been extensively used by the countries around the world.

4.1. *Putranjiva roxburghii* Wall.

4.1.1. Taxonomic status and distribution

Putranjiva roxburghii Wall. (Putranjivaceae), initially placed under Euphorbiaceae was first described and published by Nathaniel Wallich as *Putranjiva roxburghii* in Tent. Fl. Napal 61 (1826) (Govaert, 2003; Balakrishna and Chakrabarty, 2007; Krishnaraju et al., 2005; Chinmaya et al., 2009; Badole and Dighe, 2012). The plant has been named after the famous botanist William Roxburgh for recognizing his significant contribution in plant taxonomy (Haldar et al., 2009). *P. roxburghii* is reported to be widely grown all over tropical Asia for its medicinal qualities, and reported as native to Assam and tropical region of Eastern Himalaya, Indochina, Nepal, Thailand, Bangladesh, Myanmar but found distributed in Indian Subcontinent and Sri Lanka as ornamental and roadside avenue tree (Phuphathanaphong and Chayamarit, 2006; POWO). It is a deciduous, evergreen tree of about 18 m tall having grey bark with dropping branchlets. Leaves are elliptic-oblong to ovate-lanceolate, unequal-sided at the base, dark green and shining in appearance. Flowers small; male flowers dense, rounded clustered, yellowish in color; female flowers solitary or 2-3 together and green in color (Gangal et al., 2009). Seeds globose and white to mentose, stone pointed; rugose, very hard and ordinarily single are commonly called by name *Putranjiva*. *P. roxburghii* is found in the wild or cultivated in almost all parts of India (Badole et al., 2011). Roxburgh (1832) explained the name of the tree "*Pootranjeeva*" (Sanskrit word), '*Putra*' meaning a son and '*Jeeva*' means life. *P. roxburghii* is known by different local names in many languages. It is known as *Putranjiva*, *Pavitra*, *Garbhad, Sutajeevak, Kutajeeva, Apatyajeeva, Arthasadhak* and *Garbhakar* in Sanskrit, while *Putranjiva* or *Putijia* are Hindi names. Child life tree, Lucky Bean Tree, Child's amulet tree and spurious wild olive are a few of their common English names (Phuphathanaphong and Chayamarit, 2006).

4.1.2. Traditional fertility medicine and other health benefits

P. roxburghii has been traditionally used for the treatment of several health problems and also cultivated as an ornamental tree of tropical India (Chaudhary et al., 2008). The drug, *Putrajeevak Beej* is mainly derived from *P. roxburghii* which was under dispute for its homo names and synonyms for some time in India due to its literal meaning "the seed that gives life to a son". The drug has been used as a part of an ayurvedic preparation for the treatment of infertility. It is sold by the Patanjali Ayurveda Kendra, part of a trust established by Yoga guru Baba Ramdev (The Times of India, 2015). However, Patanjali Ayurveda Kendra clarified that the drug is meant for the treatment of infertility and has nothing to do with sex determination (The Times of India, 2015). Sahni (2009) also confirmed the above statement of Patanjali Ayurveda Kendra as he stated that the same has traditionally been used for the treatment of azoospermia, catarrh, and constipation. Pharmacognostical analysis of leaves, fruits, stems and roots of the plant revealed the presence of various active polyphenolic compounds which can be associated with its many therapeutic properties. These include glycosides, triterpenes, saponins, ellagic acid, gallic acid and flavonoids. Leaf extract of the plant is also studied as a biological reducing agent for the synthesis of gold nanoparticles. Two triterpenoids and four triterpenoids were isolated from the shaft bark (Garg and Mitra, 1968; Sengupta and Mukherjee, 1968). Also, a triterpene acid and a bioflavonoid were isolated from the alcoholic extract of leaves of *P. roxburghii* (Garg and Mitra, 1971). A detailed assessment of its pharmacological properties indicated its significant hypoglycaemic, anti-nociceptive, antipyretic, antiinflammatory, cytotoxic, antioxidant and antimicrobial activities. Traditionally, the fruits and leaves have been reported to be utilized for the treatment of variety of diseases like rheumatism, fever, and cold (CSIR, 2003). A biochemical literature assessment showed the presence of saponins (Hariharan, 1974), bioflavonoids (Garg and Mitra, 1971; Varshney et al., 1973), terpenoids (Sengupta and Mukherjee, 1968; Chopra et al., 1969) and sterols (Chopra et al., 1968). *Putranjiva* is an endemic plant of tropical Northeast India whose leaves, fruits and stones of fruits are given as medicine for colds and fevers, and used against rheumatism (Limbani et al., 2011). The plant is reported as astringent, refrigerant, bitter in taste, and leaves are used in the therapy of catarrh, skin disease, rheumatism, fever and sterility and decoctions are used for the treatment of cold and fever (Chopra et al., 1970). The leaves have been reported to possess analgesic, antipyretic and anti-inflammatory activity (Reanmongkol et al., 2009). *P. roxburghii* possess useful medicinal properties and has a considerable role in the traditional Ayurvedic and Unani systems of medicines (Gupta, 2016) and also referred to as uterine tonics (Rajurkar et al., 2018). The herb is believed to provide nutritional support to the uterus and maintains endometrial health, normalizing menstrual blood flow. It improves the thickness of the

endometrium and thus helps the uterus for implantation. It also modulates ovarian insufficiency, relieves anxiety, and reported to enhance and restore natural balance of the female hormone, which are very much important prior to, during and after pregnancy. Some of the more common use of the leaves and seeds are in curing inflammatory eye diseases, burning sensation, filarial, etc. More specifically, the powder form of the seeds are consumed orally for curing various ailments like ophthalmic, elephantiasis, aphrodisiac, semen disorders constipation, dysuria, infertility and diseases of female genital organs (Wantana et al., 2009; Samal and Dehury, 2017). The effective use of *Putranjiva* for antipyretics, anti-inflammatory and anti-rheumatic and also for gynaecological and fertility ailments has been mentioned in the Ayurveda. Leaf, bark and seeds of *P. roxburghii* are used as medicine and the importance of the plant in pregnancy has been highlighted in Ayurvedic classics. The powdered form of seeds (dose of 1-3 g) along with milk improves the sperm count in males and assists in maintaining the fetus in pregnant women. The leaf extracts and bio-oil extracted from seeds are mostly utilized in Ayurveda, Herbal and Unani medications (Supriya et al., 2017). Badole and Dighe (2012) reported that to promote health, nuts are strung by parents and put around the necks of their children. Seeds are fresh and sour. It is ophthalmic emetic, aphrodisiac, anti-seditious and diuretic. It has been used for conventional health applications such as treating mouth and stomach ulcers, hot swellings, smallpox, ophthalmopathy, hyperemesis, elephantiasis, impairment, strangury, azoospermia, usual termination and infertility (Sengupta and Mukherjee, 1968; Varshney et al., 1973; Rajurkar et al., 2018). An ethnobotanical survey at Karandamalai (South Eastern Ghats) in Tamil Nadu revealed the potential application of bark of *Putranjiva* in combination with leaves of *Pterospermum suberifolium* in healing broken bones (Kottaimuthu, 2008).

4.2. *Diplocyclos palmatus* (L.) C. Jeffrey

4.2.1. Taxonomic status, distribution range and folklore claim as fertility medicine

The *Diplocyclos palmatus* (Family Cucurbitaceae) was first described and published as *Bryonia palmata* (now heterotypic synonyms) by Carolus Linnaeus in *Species Plantarum* 2: 1012 (1753). Later, C. Jeffrey transferred this species from genus *Bryonia* to *Diplocyclos* and thus published a *Diplocyclos palmatus* (L.) C. Jeffrey in Kew Bulletin 15: 352 (1962). Recently, Balkrishna et al (2021) supported *Diplocyclos palmatus* as correct identity for the famous Ayurvedic fertility drug sources climber "*Shivalingi"* which is found native to India and also found widely distributed in South East Asia and Africa. Earlier, there was confusion among the systematic botanists and pharmacobotanists due which they treated *Bryonia laciniosa* L. as correct identity for the *Shivalingi*. However, the *Bryonia laciniosa* is again a synonym for *Capaponia laciniosa* (L.) C. Jeffrey which is reported to be only native to Jamaica Island by C. Jefferey published in Kew Bulletin 15: 346 (1962) and which is not found distributed in India. Now as per the claim of Balkrishna et al (2021) through Indian folklore information and taxonomic literatures, the correct taxonomic identity for *Shivalingi* is established as *Diplocyclos palmatus* (L.) C. Jefferey but not the *Bryonia laciniosa* L. or *Cayaponia laciniosa* (L.) C. Jeffrey as considered earlier as these two are entirely a different species. *Diplocyclos palmatus* (L.) C. Jefferey of Cucurbitaceae, popularly known as *Shivalingi* in India is reported to be a climber native to Assam and tropical India (Balkrishna, 2021; POWO) and it is reported as one of the significant crude drug sources used in the Indian traditional system of medicine from ancient times, particularly in Ayurveda. Other heterotypic synonyms available for *Diplocyclos palmatus* (L.) C. Jeffrey are *Bryonia palmata* L. and *Coccinia palmata* (L.) M. Roem. It is a weak climber found distributed in tropical India, tropical Nepal, Sri Lanka, Indo-China, South China, Pakistan, Indonesia, Philippines, Papua New Guinea, and some parts of central and West Africa (POWO; Balkrishna et al., 2021). It has a considerable reputation as a potent adjunct in the treatment of various ailments such as jaundice, inflammation and fever (Kirtikar and Basu, 1935; Paul and Raj, 1960). In India it is found distributed in Madhya Pradesh, Uttar Pradesh, Gujrat, and Uttrakhand. The plant is an annual climber having bright red fruits, and it has been reported to be of high medicinal value. The seeds of *D. palmatus* are yellowish-brown, and since the upper surface of seeds has making and morphology with resembles that of *Shivlinga* (Phallus of Lord Shiva in Hindu mythology) and hence called "*shivlingi*" (Panda, 2004). The naturally propagated by seeds, is generally present throughout India on edges and bushes up to 1200 m elevation, and locally the fruits of *D. palmatus* is known as *Shivalingakkaya* in Malayalam, *Lingatondikai* in Kannada, *Lingadonda* in Telugu, *Shivalingakkay* in Tamil and *Shivalingi* in Gujarathi and Marathi and Lollipop climber, as common English name (Warrier et al., 2006). The plant has been reported as antiinflammatory, anti-diabetic, anti-microbial, analgesic and anti-pyretic activities (Sivakumar et al., 2004; Singh et al., 2009; Chauhan and Dixit, 2010; Gupta and Wagh, 2014; Patel et al., 2015; Singh, 2017). Traditional healers of *Gulgul* village, Chhattisgarh suggests the use of 3-4 seeds once daily by women in empty stomach for 1 to 2 months to get a male child (Wathurkar et al., 2019). The leaf extract of the plant has been reported to be used against cathartic and hot aqueous extract of the roots and seeds have been reported effective for conception in barren women (Kirtikar and Basu, 1935).

4.2.2. Bioactive principles, pharmacological activities and traditional fertility therapy

The occurrence of bitter principle bryonin, saponin, punicic acid, goniothalamine, and glucomannan has been reported in this plant (Gowrikumar et al., 1981; Mosaddik et al., 2000; Saxena et al., 2004; Singh and Malviya, 2006). *Diplocyclos palmatus* has been used as a trivial pharmaceutical since long in India (Paul and Raj, 1960). Goniothalamin, punicic acid and lipids have been isolated previously from the whole plant of *D. palmatus* (Mosaddik et al., 2000; Bonyadi et al., 2009). The plant showed many pharmacological activities like analgesic, antipyretic, anticonvulsant, antimicrobial, cytotoxic, antiasthmatic, anti-inflammatory and antifertility. The seeds of *Shivlingi* are potentially contraceptive when used in combination with ginger (dry), pepper, *Putrajivi,* Root bark of *Vata* (*Ficus bengalensis*) and milk (Rajesh and Moyna, 2008). In another studies, abortifacient action of *shivlingi* seeds have also been reported. The *shivlingi* seeds if combined with an equal amount of *ashwagandha* roots and consumed with sugar and milk, *Bhawda Amala* acts as an abortifacient (Sharma, 1995; Patil and Bhaskar, 2006). On the other side, *Shivlingi beej* have been reported to be used for treatment of female infertility. It is a uterine tonic for women suffering from infertility as improves the chances of conception in them. It is one of the important medicinal climbers mentioned in the Ayurveda which is mainly used for enhancing fertility when used with *Putranjiva Beej* or seed. Many traditional uses for adenopathy, ague, asthma, bronchitis, carbuncles, cholera, colic, consumption, convulsions, cough, delirium, fertility, headache, megalospleny, paralysis, phthisis, snake bite are also reported for this plant species (Gupta et al., 2003; Bonyadi et al., 2009). It is widely employed as an important herbal drug for the treatment of gastrointestinal, respiratory, rheumatic and metabolic disorders, as well as for liver and infectious diseases (Gabrielian and Gevorgovich, 1997; Panda, 2004; Acharya, 2007). It is also identified to have antitumor effects used among the tribal population of south India (Sivakumar et al., 2005). The whole plant of *D. palmatus* is suggested traditionally for inflammation (Gupta et al.,2003) inducing diuresis and as a tonic (Kirtikar and Basu, 1935). Increased spermatogenesis and a significant increase in sperm count in the epididymis of the male albino rats with the concurrent increase in serum testosterone and luteinizing hormone have been reported with the use of *shivlingi* seeds. The study clearly reflects androgenic activity and its effects on the hypothalamic-pituitary-gonadal axis (Chauhan and Dixit, 2010). The ethanolic extract and saponin fraction of the seeds of this plant were administered to diabetic rats and compared with the insulin administration on rats serving as the positive control. The study revealed the efficacy of *D. palmatus* seed extract in the amelioration of diabetes and its associated complications (Patel et al., 2012).

5. Conclusion and future scopes

Plants as medicinal agents predates human history and are inseparable part of human life. People with growing concern and knowledge shifted their focus to traditional medicinal plants for effective treatment of various ailments. May it be for general health or for reproductive related issues which has been seeing catastrophic rise in contemporary world; plants as a medicine have always been used by the indigenous tribal communities in India and the rest of the world as a primary source of medication for treatment of local ailments due to its easy accessibility, less side effects, cheap and affordable for the low-income group rural population across the world. To address the very sensitive yet alarming issue like infertility, the world population is relying more on the herbal therapy. Two of such medicinal plants, *P. roxburghii* and *D. palmatus* have been reported with numerous health benefits. In India, many of the infertility related problems are tackled using these two medicinal plants. From uterine tonic to servicing as a medicine to increase the chances of conception or help conceive, these two plants with its various phytochemicals in them are stated to be an aid to alleviate number of reproductive related problems like azoospermia, aphrodisiac, menstrual disorder, semen disorders, infertility, diseases of female genital organs, etc. The plant *Shivlingi* is also believed to help give birth to a male child when its seed is consumed by female in empty stomach for 1-2 months. The co administration of the two medicinal plants *(P. roxburghii and D. palmatus)* is also reported to enhance fertility.

Literature evidences suggested that these two medicinal plants are extensively used by people around the globe especially by local communities in India in their rural healthcare system. No doubt there are several reports stating the benefits of these two medicinal plants in various reproductive-related aspects but there is still a need for further scientific studies to validate and justify the statements of published literatures and folklore claims made by the traditional herbal practitioners or local communities. Only few reports are available to date on these two important traditional plants of India with particularly reference to their reproductive health benefits. Further, there is no reports available to date on the coadministration of these two medicinal plants to enhance fertility benefits in human. To conclude, extensive research is still necessary for the validation and formulation of fertility drugs from these plants *(P. roxburghii and D. palmatus)* along with a proper screening of phytosteroids and other phytocompounds to provide hope to couples dealing with infertility-related health problems.

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Author's Contributions

PB, MY and PK conceptualized the article and wrote the first draft of the manuscript. MY, PK and BL edited the manuscripts. All the authors read and approved the final version of the manuscript.

Conflict of Interests

The authors report no conflict of interest.

References

Abma JC, Chandra A, Mosher WD, Peterson LS and Piccinino LJ. 1997. Fertility, family planning, and women's health: new data from the 1995 National Survey of Family Growth. Vital and Health statistics Vol. 19, Series 23. Pp. 1–114.

Acharya D. 2007. *Shivlingi*: A common but important twine in Patalkot. American Chronicles. Oct. 14. http://www.americanchronicle.com/articles/view/40216

Agarwal A. 2005. Critical issues in Quality control of Herbal products. Pharma Times 37(6): 9-11.

Aitken RJ, West K and Buckingham D. 1994. Leukocytic infiltration into the human ejaculate and its association with semen quality, oxidative stress, and sperm function. Journal of Andrology 15(4): 343–352.

Aittomäki K, Lucena JL, Pakarinen P, Sistonen P, Tapanainen J, Gromoll J, Kaskikari R, Sankila EM, Lehväslaiho H, Engel AR et al. 1995. Mutation in the follicle-stimulating hormone receptor gene causes hereditary hypergonadotropic ovarian failure. Cell 82(6):959–968. https://doi.org/10.1016/0092-8674(95)90275-9

Araoye MO. 2003. Epidemiology of infertility: social problems of the infertile couples. West African Journal of Medicine 22(2): 190–196. https://doi.org/10.4314/wajm.v22i2.27946

Augood C, Duckitt K and Templeton AA. 1998. Smoking and female infertility: a systematic review and meta-analysis. Human reproduction (Oxford, England) 13(6):1532–1539. https://doi.org/10.1093/humrep/13.6.1532

Badole MR and Dighe VV. 2012. Synthesis of Gold Nano particles using *Putranjiva roxburghii* Wall. leaves extract. International Journal of Drug Discovery and Herbal Research 2(1): 275-278.

Badole N, Dighe V and Charegaonkar G. 2011. Simultaneous quantification of β-amyrin and stigmasterol in *Putranjiva roxburghii* Wall. by high-performance thin-layer chromatography. International Journal of Pharmacy and Biological Sciences 2: 346-352.

Baker M. 1996. Fur rubbing: use of medicinal plants by capuchin monkeys (*Cebus capucinus*). American Journal of Primatology 38(3):263-270.

Balakrishnan NP and Chakrabarty T. 2007. *The family Euphorbiaceae in India. A synopsis of its profile, taxonomy and bibliography*. Bishen Singh Mahendra Pal Singh, Dehra Dun. Pp. 1-500.

Balkrishna A, Singh A, Shankar R, Mishra RK, Srivastava A, Joshi B and Chauhan A. 2021. Establishing the correct botanical identity of *Śivaliṅgī* plant in India: A critical analysis based on various literatures. Journal of Medicinal Plants Studies 9 (3): 156-167

Balandrin MF, Klocke JA, Wurtele ES and Bollinger WH. 1985. Natural plant chemicals: sources of industrial and medicinal materials. Science (New York, N.Y.) 228(4704):1154–1160. https://doi.org/10.1126/science.3890182

Barnes PM, Bloom B and Nahin RL. 2008. Complementary and alternative medicine use among adults and children: United States, 2007. National health statistics reports 12: 1–23.

Bergström S. 1992. Reproductive failure as a health priority in the Third World: a review. East African Medical Journal 69(4): 174–180.

Bisset NG and Wichtl M. 1994. Herbal Drugs and Phytopharmaceuticals. Medpharm GmbH Scientific Publishers, Stuttgart, CRC Press, Boca Raton 91-95.

Bodeker G, Ong CK, Grundy CK, Burford G and Shein K. 2005. WHO Global Atlas of Traditional, Complementary and Alternative Medicine. Geneva, Switzerland: World Health Organization. Kobe, Japan: WHO Centre for Health Development. https://apps.who.int/iris/handle/10665/43108

Boivin J, Bunting L, Collins JA and Nygren KG. 2007. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. Human reproduction (Oxford, England) 22(6):1506–1512.

Bonyadi RE, Awad V and Nirichan KB. 2009. Antimicrobial activity of the ethanolic extract of *Bryonopsis laciniosa* leaf, stem, fruit and seed African Journal of Biotechnology 8(15): 3565-3567.

Broekmans FJ, Kwee J, Hendriks DJ, Mol BW and Lambalk CB. 2006. A systematic review of tests predicting ovarian reserve and IVF outcome. Human Reproduction Update 12(6):685–718. https://doi.org/10.1093/humupd/dml034

Bromer JG and Seli E. 2008. Assessment of embryo viability in assisted reproductive technology: shortcomings of current approaches and the emerging role of metabolomics. Current Opinion in Obstetrics & Gynecology 20(3):234–241.

Budhwar S, Singh V, Verma P and Singh K. 2017. Fertilization failure and gamete health: Is there a link?. Frontiers in bioscience (Scholar edition) 9(3):395–419. https://doi.org/10.2741/s494

Cedars MI, Taymans SE, DePaolo LV, Warner L, Moss SB and Eisenberg ML. 2017. The sixth vital sign: what reproduction tells us about overall health. Proceedings from a NICHD/CDC workshop. Human Reproduction Open 2017(2):1-8.

Chaudhary NS, Shee C, Islam A, Ahmad F, Yernool D, Kumar P and Sharma AK. 2008. Purification and characterization of a trypsin inhibitor from *Putranjiva roxburghii* seeds. Phytochemistry 69(11):2120–2126.

Chauhan NS and Dixit VK. 2010. Effects of *Bryonia laciniosa* seeds on sexual behaviour of male rats. International journal of impotence research 22(3):190–195.

Chinmaya A, Sudharshan SJ, Valleesha NC, Kekuda TR, Rajeshwara AN, Murthuza S and Praveen Kumar SV. 2009. Phytoconstituents and antioxidant activity of *Drypetes roxburghii* Wall, *Coscinium fenestratum* Colebr and *Nardostachys jatamansi* DC. Global Journal of Pharmacology 3(1): 53-58.

Chopra GR, Jain AC and Seshadri TR. 1968. Steroidal and triterpenoidal components of the leaves of *Putranjiva roxburghii*. Current Science 37: 301-304.

Chopra GR, Jain AC and Seshadri TR. 1969. Isolation and structure of putrolic acid-a new triterpenic seco-acid, from the stem-bark of *Putranjiva roxburghii*. Current Science 38 (5): 101-102.

Chopra GR, Jain AC, Seshadri TR and Sood GR. 1970. Chemical components of the leaves and root-bark of *Putranjiva roxburghii*. Indian Journal of Chemistry 8: 776- 778.

Chopra RN, Nayar SL and Chopra IC. 1956. Glossary of Indian Medicinal Plants. Council of Scientific and Industrial Research, New Delhi, India. Pp.15-180.

Cirico TL and Omaye ST. 2006. Additive or synergetic effects of phenolic compounds on human low density lipoprotein oxidation. Food and chemical toxicology: an international journal published for the British Industrial Biological Research Association 44(4):510–516. https://doi.org/10.1016/j.fct.2005.08.025

Comhaire FH 1987. *Towards more objectivity in diagnosis and management of male infertility*. In: World Health Organization Task Force on the Diagnosis and Treatment of Infertility. Blackwell Scientific, Oxford. Pp 1-53.

Cox PA. 1990. Ethnopharmacology and the search for new drugs. Ciba Foundation symposium 154: 40–55.

Crosignani PG, Collins J, Cooke ID, Diczfalusy E and Rubin B. 1993. Recommendations of the ESHRE workshop on 'Unexplained Infertility'. Anacapri, August 28-9, 1992. Human Reproduction (Oxford, England) 8(6): 977–980.

Croxtall JD and McKeage K. 2011. Corifollitropin alfa: a review of its use in controlled ovarian stimulation for assisted reproduction. BioDrugs: Clinical Immunotherapeutics, Biopharmaceuticals and Gene Therapy 25(4): 243–254.

Dahanukar SA, Kulkarni RA and Rege NN. 2000. Pharmacology of medicinal plants and natural products. Indian Journal of Pharmacology 32: S81-S118.

de Lamirande E, Leduc BE, Iwasaki A, Hassouna M and Gagnon C. 1995. Increased reactive oxygen species formation in semen of patients with spinal cord injury. Fertility and Sterility 63(3): 637–642.

Dierich A, Sairam MR, Monaco L, Fimia GM, Gansmuller A, LeMeur M and Sassone-Corsi P. 1998. Impairing follicle-stimulating hormone (FSH) signaling in vivo: targeted disruption of the FSH receptor leads to aberrant gametogenesis and hormonal imbalance. Proceedings of the National Academy of Sciences of the United States of America 95(23): 13612–13617. https://doi.org/10.1073/pnas.95.23.13612

Dohle GR, Colpi GM, Hargreave TB, Papp GK, Jungwirth A, Weidner W and EAU Working Group on Male Infertility. 2005. EAU guidelines on male infertility. European Urology 48(5): 703–711. https://doi.org/10.1016/j.eururo.2005.06.002

Evans WC. 2002. *Trease and Evans Pharmacognosy*, 15th Edition. W.B Sauders Company Ltd, London. Pp. 230-240.

Farnsworth NR, Akerele O, Bingel AS, Soejarto DD and Guo Z. 1985. Medicinal plants in therapy. Bulletin of the World Health Organization. 63(6): 965–981.

Farnsworth NR. 1990. The Role of Ethno Pharmacology in Drug Development. Ciba Foundation Symposium 154. Bioactive Compounds from Plants. John Wiley & Sons, Baffins Lane, Chichester (England) 2-21.

Fransworth NR. 1994. Ethnopharmacology and Drug Development. In: Chadwick DJ and Marsh J (Ed.), *Ethnobotany and the Search for New Drugs*. CIBA Foundation Symposium 185, John Wiley and Sons, Chichester, New York. Pp. 42-51.

Gabrielian SE and Gevorgovich A. 1997. *Bryonia*, as novel plant adoptogen, for prevention and treatment of stress induced disorders. Promising Research Abstract PRA. 5003:1-8.

Gangal S, Sharma S and Rauf A. 2009. *Putranjiva roxburghii* seeds: oil content and fatty acid composition during different stages of seed maturity. Journal of Pharmacy Research 2(11): 1666–1668.

Garg HS and Mitra CR. 1968. *Putranjiva roxburghii* Wall. – II Triterpenes of the trunk bark. Phytochemistry 7: 2053–2055.

Garg HS and Mitra CR. 1971. Putraflavone, a new biflavonoid from *Putranjiva roxburghii*. Phytochemistry 10: 2787-2791.

Gerrits T. 1997. Social and cultural aspects of infertility in Mozambique. Patient education and counseling 31(1): 39–48. https://doi.org/10.1016/s0738-3991(97)01018-5

Glander KE. 1994. Nonhuman primate self-medication with wild plant foods. In: Etkin NL (Ed.), *Eating on the Wild side: The Pharmacologic, Ecological, and Social Implications of Using Noncultigens*. University of Arizona Press, Tuscon. Pp. 239-256.

Govaerts R. 2003. World Checklist of Selected Plant Families Database in ACCESS: 1-216203. The Board of Trustees of the Royal Botanic Gardens, Kew.

Gowrikumar G, Mani VV, Chandrasekhararao T, Kaimal TN and Lakshminarayana G. 1981. *Diplocyclos palmatus* L: A new seed source of punicic acid. Lipids 16(7): 558-559.

Gupta M, Mazumdar UK, Sivakumar T, Vamsi ML, Karki SS, Sambathkumar R and Manikandan L. 2003. Evaluation of anti-inflammatory activity of chloroform extract of *Bryonia laciniosa* in experimental animal models. Biological & Pharmaceutical Bulletin 26(9):1342–1344. https://doi.org/10.1248/bpb.26.1342

Gupta M. 2016. A review of pharmacological properties, pharmacognosy and therapeutic actions of *Putranjiva roxburghii* Wall. (Putranjiva). International Journal of Herbal Medicine 4(6): 104-108.

Gupta P and Wagh RD. 2014. A review on morphology, phytochemistry, pharmacology and folklore uses of *Diplocyclos palmatus* (L.) Jeffry. International Journal of Pharmacy and Life Sciences 5:3622-3626.

Håkonsen LB, Ernst A and Ramlau-Hansen CH. 2014. Maternal cigarette smoking during pregnancy and reproductive health in children: a review of epidemiological studies. Asian Journal of Andrology 16(1):39–49. https://doi.org/10.4103/1008-682X.122351

Halberstein RA. 2005. Medicinal plants: historical and cross-cultural usage patterns. Annals of Epidemiology 15(9):686–699.

Haldar SK, Ghosh BB and Nag A. 2009. Utilization of unattended *Putranjiva roxburghii* non-edible oil as fuel in a diesel engine. Renewable Energy 34: 343–347.

Hariharan V. 1974. Structures of putranosides from the seed-coats of *Putranjiva roxburghi*. Indian Journal of Chemistry 12: 447-449.

Hassan BAR. 2012. Medicinal Plants (Importance and Uses). Pharmaceutica Analytica Acta 3 (10): 1000e139.

Hayashi Y, Saitou M and Yamanaka S. 2012. Germline development from human pluripotent stem cells toward disease modeling of infertility. Fertility and Sterility 97(6):1250–1259. https://doi.org/10.1016/j.fertnstert.2012.04.037

Hollos M. 2003. Profiles of infertility in southern Nigeria: women's voices from Amakiri. African Journal of Reproductive Health 7(2):46–56.

Homan GF, Davies M and Norman R. 2007. The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: a review. Human Reproduction Update 13(3):209–223.

Huffman MA. 1997. Current evidence for self-medication in primates: A multidisciplinary perspective. American Journal of Physical Anthropology 104(S25): 171–200.

Hughes EG and Brennan BG. 1996. Does cigarette smoking impair natural or assisted fecundity? Fertility and Sterility 66(5):679–689. https://doi.org/10.1016/s0015-0282(16)58618-x

Inhorn MC and van Balen F. 2002. *Infertility around the Globe: New Thinking on Childlessness, Gender, and Reproductive Technologies*. Berkeley, CA: University of California Press. http://www.jstor.org/stable/10.1525/j.ctt1ppfk5

Iwasaki A and Gagnon C. 1992. Formation of reactive oxygen species in spermatozoa of infertile patients. Fertility and sterility 57(2): 409–416. https://doi.org/10.1016/s0015-0282(16)54855-9

Jeffrey C.1962. *Diplocyclos palmata* (L.) C. Jeffrey. Kew Bulletin 15: 352 (1962).

Jones R, Mann T and Sherins R. 1979. Peroxidative breakdown of phospholipids in human spermatozoa, spermicidal properties of fatty acid peroxides, and protective action of seminal plasma. Fertility and Sterility 31(5):531–537. https://doi.org/10.1016/s0015-0282(16)43999-3

Joshi B, Sah GB, Basnet BB, Bhatt MR, Sharma D, Subedi K, Pandey J and Malla R. 2011. Phytochemical extraction and antimicrobial properties of different medicinal plants: *Ocimum sanctum* (Tulsi), *Eugenia caryophyllata* (Clove), *Achyranthes bidentata* (Datiwan) and *Azadirachta indica* (Neem). Journal of Microbiology and Antimicrobials 3(1): 1-7.

Josso N, Racine C, di Clemente N, Rey R and Xavier F. 1998. The role of anti-Müllerian hormone in gonadal development. Molecular and Cellular Endocrinology 145(1-2): 3–7. https://doi.org/10.1016/s0303-7207(98)00186-5

Jungwirth A, Giwercman A, Tournaye H, Diemer T, Kopa Z, Dohle G, Krausz C and European Association of Urology Working Group on Male Infertility. 2012. European Association of Urology guidelines on Male Infertility: the 2012 update. European Urology 62(2):324–332. https://doi.org/10.1016/j.eururo.2012.04.048

Kala CP, Dhyani PP and Sajwan BS. 2006. Developing the medicinal plants sector in northern India: challenges and opportunities. Journal of Ethnobiology and Ethnomedicine 2(32). https://doi.org/10.1186/1746-4269-2-32

Kamboj VP. 2000. *Herbal Medicine*. Current Science 78:35-39.

Kamel RM. 2013. Assisted reproductive technology after the birth of louise brown. Journal of Reproduction and Infertility 14(3):96–109.

Kendler BS. 1987. Garlic (*Allium sativum*) and onion (*Allium cepa*): a review of their relationship to cardiovascular disease. Preventive medicine 16(5):670–685. https://doi.org/10.1016/0091-7435(87)90050-8

Kirtikar KR and Basu BD. 1935. *Indian Medicinal Plants, 2nd Ed.* The Indian Press, Allahabad. Pp. 1158—1159.

Kottaimuthu R. 2008. Ethnobotany of the Valaiyans of Karandamalai, Dindigul District, Tamil Nadu, India. Ethnobotanical Leaflets 12: 195–203.

Krishnaraju AV, Rao TVN, Sundararaju D, Vanisree M, Tsay H-S and Subbaraju GV. 2005. Assessment of Bioactivity of Indian Medicinal Plants Using Brine Shrimp (Artemia salina) Lethality Assay. International Journal of Applied Science & Engineering 2:125-134.

Kumar D. 2005. The tribal literacy disparity in India. Current Science 88(5): 676.

Kumar TR, Wang Y, Lu N and Matzuk MM. 1997. Follicle stimulating hormone is required for ovarian follicle maturation but not male fertility. Nature Genetics 15(2):201–204. https://doi.org/10.1038/ng0297-201

Leke RJ, Oduma JA, Bassol-Mayagoitia S, Bacha AM and Grigor KM. 1993. Regional and geographical variations in infertility: effects of environmental, cultural, and socioeconomic factors. Environmental Health Perspectives 101(Suppl 2): 73–80.

Leslie C and Young A. 1992. *Paths to Asian Medical Knowledge*. University of California Press, Berkely, California.

Limbani RK, Bandhiya HM, Dedakia AS, Desai TR, Patel VL and Pandya DJ. 2011. Pharmacognostic and phytochemical evaluation of leaves of *Putranjiva roxburghii*. International Journal of Comprehensive Pharmacy 2(11):1-3.

Linnaeus C. 1753. *Species Plantarum* 2: 1012 (1753). Stockholm: Impensis Laurentii Salvii.

Lunenfeld B. 2004. Historical perspectives in gonadotrophin therapy. Human Reproduction Update 10(6):453–467. https://doi.org/10.1093/humupd/dmh044

Macaluso M, Wright-Schnapp TJ, Chandra A, Johnson R, Satterwhite CL, Pulver A, Berman SM, Wang RY, Farr SL and Pollack LA. 2010. A public health focus on infertility

prevention, detection, and management. Fertility and Sterility 93(1). https://doi.org/10.1016/j.fertnstert.2008.09.046

Macklon NS, Stouffer RL, Giudice LC and Fauser BC. 2006. The science behind 25 years of ovarian stimulation for in vitro fertilization. Endocrine Reviews 27(2):170–207. https://doi.org/10.1210/er.2005-0015

Mashelkar RA. 2008. Second World Ayurveda Congress (Theme: Ayurveda for the Future)-Inaugural Address: Part III. Evidence-based Complementary and Alternative Medicine : eCAM 5(4): 367–369. https://doi.org/10.1093/ecam/nen015

Masood E. 1997. 'Medicinal plants threatened by over-use'. Nature 385(6617): 570. https://doi.org/10.1038/385570a0

Matzuk MM and Lamb DJ. 2002. Genetic dissection of mammalian fertility pathways. Nature Cell Biology. 4 Suppl: s41–s49. https://doi.org/10.1038/ncb-nm-fertilityS41

McCaleb RS. 1997. Medicinal Plants for Healing the planet: Biodiversity and Environmental Health In: Grifo F and Rosenthal J (Ed.), *Biodiversity and Human Health*. Revised ed. Island Press.

Meenal S, Kubde S, Khadabadi S, Farooqui IA and Deore SL. 2010. Phytochemistry, pharmacognosy and pharmacological studies. Report and Opinion 2(12):24-31.

Meserole L. 2001. Western herbalism. In: Micozzi M (Ed.), *Fundamentals of Complementary and Alternative Medicine*. 2nd ed. New York: Churchill Livingstone 128–137.

Mosaddik MA, Ekramul HM and Abdur RM. 2000. Goniothalamin from *Bryonopsis laciniosa* Linn (Cucurbiataceae). Biochemical Systematics and Ecology 28(10): 1039–1040. https://doi.org/10.1016/s0305-1978(00)00017-x

Mukherjee PW. 2002. Quality Control of Herbal Drugs: An Approach to Evaluation of Botanicals. Business Horizons Publishers, New Delhi, India.

Naranjo P. 1995. The urgent need for the study of medicinal plants. In: Schultes RE and Reis S von (Ed.), *Ethnobotany- Evolution and Discipline*. Timber Press, United States of America. Pp. 362-368.

Nijveldt RJ, van Nood E, van Hoorn DE, Boelens PG, van Norren K and van Leeuwen PA. 2001. Flavonoids: a review of probable mechanisms of action and potential applications. The American Journal of Clinical Nutrition 74(4):418–425. https://doi.org/10.1093/ajcn/74.4.418

Ochsendorf FR and Fuchs J. 1993. Oxidative imbalance in male infertility. In: Fuchs J and Packer L (Ed.), *Oxidative stress in dermatology*. Dekker, New York-Basel-Hong Kong, Pp 481-529.

O'Hara M, Kiefer D, Farrell K and Kemper K. 1998. A review of 12 commonly used medicinal herbs. Archives of Family Medicine 7(6):523–536.

Olmedo SB, Rawe VY, Nodar FN, Galaverna GD, Acosta AA and Chemes HE. 2000. Pregnancies established through intracytoplasmic sperm injection (ICSI) using spermatozoa with dysplasia of fibrous sheath. Asian Journal of Andrology 2(2):125–130.

Padron OF, Brackett NL, Sharma RK, Lynne CM, Thomas Jr. AJ and Agarwal A. 1997. Seminal reactive oxygen species and sperm motility and morphology in men with spinal cord injury. Fertility and sterility 67(6): 1115–1120. https://doi.org/10.1016/s0015-0282(97)81448-3

Panda H. 2004. Handbook on Herbal Medicine. National Institute of Industrial Research: New Delhi. Pp 478.

Pandey MM, Rastogi S and Rawat AKS. 2008. Indian herbal drug for general healthcare: an overview. The Internet Journal of Alternative Medicine 6(1): 3.

Papreen N, Sharma A, Sabin K, Begum L, Ahsan S.K and Baqui A.H. 2000. Living with infertility: experiences among Urban slum populations in Bangladesh. Reproductive health Matters 8(15): 33–44. https://doi.org/10.1016/s0968-8080(00)90004-1

Parfitt R.T. 1978. *Drug Discovery, Design or Serendipity*. An Inaugural Lecture Series. University of Bath, U.K.

Patel S, Santani D, Shah M and Patel V. 2012. Anti-hyperglycemic and Anti-hyperlipidemic Effects of *Bryonia laciniosa* Seed Extract and its Saponin Fraction in Streptozotocin-induced Diabetes in Rats. Journal of Young Pharmacists 4(3):171–176. https://doi.org/10.4103/0975-1483.100024

Patel SB, Santani D, Patel V and Shah M. 2015. Anti-diabetic effects of ethanol extract of *Bryonia laciniosa* seeds and its saponins rich fraction in neonatally streptozotocin-induced diabetic rats. Pharmacognosy Research 7(1):92–99. https://doi.org/10.4103/0974-8490.147217

Patil HM and Bhaskar VV. 2006. Medicinal knowledge system of tribal's of Nandurbar district, Maharashtra, Indian Journal of Traditional Knowledge 5(3): 327-330.

Patwardhan B, Warude D, Pushpangadan P and Bhatt N. 2005. Ayurveda and traditional Chinese medicine: a comparative overview. Evidence-based Complementary and Alternative Medicine : Ecam 2(4):465–473. https://doi.org/10.1093/ecam/neh140

Paul V and Hem Raj KK. 1960. Chemical investigation of *Bryonopsis lacinosa* fruit oil. Proceedings of the National Academy of Sciences of the USA 29:218-21.

Phillips OL and Meilleur BA. 1998. Usefulness and economic potential of the rare plants of the United States: a statistical survey. Economic Botany 52: 57–67.

Phuphathanaphong L and Chayamarit K. 2006. *Flora of Thailand Euphorbiaceae*. National Herbarium of the Nederland 336: 1877–87.

Plotkin MJ. 2003. *Ethnobotanical Leaflets*: Medicine Quest Vol. 2003 (1): 30 – 180. https://opensiuc.lib.siu.edu/ebl/vol2003/iss1/18

POWO. Plant of the World Online. Hosted by Royal Botanic Garden, Kew, UK. https://powo.science.kew.org/taxon/urn:lsid:ipni.org:names:291813-1

Rajesh S and Moyna C. 2008. Indigenous medicine used for treatment of gynecological disorders by tribal of Chhattisgarh, India. Plants Research 2(12): 356-360.

Rajurkar SS, Jadhav ND, Ballurkar BV and Rajurkar SR. 2018. *Putranjiva roxburghii*: Medicated feed as uterine tonic in wistar rats. International Journal of Veterinary Sciences and Animal Husbandry 3(5): 16-22.

Reanmongkol W, Noppapan T and Subhadhirasakul S. 2009. Antinociceptive, antipyretic, and anti-inflammatory activities of *Putranjiva roxburghii* Wall. leaf extract in experimental animals. Journal of Natural Medicines 63(3):290–296.

Richards SC. 2002. "Spoiling the womb": definitions, aetiologies and responses to infertility in north west province, Cameroon. African Journal of Reproductive Health 6(1):84–94.

Ross JA and Kasum CM. 2002. Dietary flavonoids: bioavailability, metabolic effects, and safety. Annual review of nutrition 22:19–34.

Roupa Z, Polikandrioti M, Sotiropoulou P, Faros E, Koulouri A, Wozniak G and Gourni M. 2009. Causes of infertility in women at reproductive age. Health Science 3(2): 80-87.

Rowe PJ, Comhaire FH, Hargreave TB and Mellows HJ. 1993. WHO Manual for the Standardized Investigation and Diagnosis of the Infertile Couple. Cambridge University Press, Cambridge.

Roxburgh W. 1832. *Flora of India* Serampore 3: 767. W.Thacker and CO., Calcutta.

Sahni KC. 2009. *The Book of Indian Tree*. 2nd Ed. New Delhi: Himalaya Publishing House 285-9.

Samal J and Dehury RK. 2017. *Putranjiva roxburghii* Wall: The controversies and the concurrences. International Journal of Green Pharmacy 10(4): s254-s256.

Saurabh G and Kaushal C. 2011. Pharmaceutical Solid Polymorphism in Abbreviated New Drug Application (ANDA) – A Regulatory Perspective. Journal of Chemical and Pharmaceutical Research 3(3): 6-17.

Saxena N, Balyari N and Srivastva A. 2004. Pharmacological studies of novel pharmaceutical saponin molecules of seeds of *Bryonia laciniosa*. IUPAC. International conference on biodiversity, natural product chemistry and medicinal applications 26 (31): 368.

Sengupta P and Mukherjee J. 1968. Terpenoids and related compounds XI; The structure of roxburgholone, a new triterpenoid constituent of *Putranjiva roxburghi*. Tetrahedron 24: 6259-6264.

Shah K, Sivapalan G, Gibbons N, Tempest H and Griffin DK. 2003. The genetic basis of infertility. Reproduction (Cambridge, England) 126(1):13–25.

Shankar D and Ved DK. 2003. A balanced perspective for management of Indian medicinal plants. Indian Forester 129 (2): 275-288.

Sharma PV. 1995. *Introduction to dravyaguna (Indian Pharmacology)*. Chaukhamba Orientalia: Varanasi, Pp. 590-592.

Sharma RK and Agarwal A. 1996. Role of reactive oxygen species in male infertility. Urology 48(6):835–850. https://doi.org/10.1016/s0090-4295(96)00313-5

Sheiner EK, Sheiner E, Hammel RD, Potashnik G and Carel R. 2003. Effect of occupational exposures on male fertility: literature review. Industrial Health 41(2):55–62. https://doi.org/10.2486/indhealth.41.55

Simoni M, Gromoll J and Nieschlag E. 1997. The follicle-stimulating hormone receptor: biochemistry, molecular biology, physiology, and pathophysiology. Endocrine Reviews 18(6):739–773. https://doi.org/10.1210/edrv.18.6.0320

Singh V and Malviya T. 2006. A non-ionic glucomannan from the seeds of an indigenous medicinal plant: *Bryonia lacinosa* 64(3): 481–483.

Singh V, Malviya T, Tripathi DN and Naraian U. 2009. 'An Escherichia coli antimicrobial effect of arabinoglucomannan from fruit of *Bryonia laciniosa*', Carbohydrate Polymers 75(3): 534–537.

Sivakumar T, Perumal P, Kumar RS, Vamsi ML, Gomathi P, Mazumder UK and Gupta M. 2004. Evaluation of analgesic, antipyretic activity and toxicity study of *Bryonia laciniosa* in mice and rats. The American Journal of Chinese Medicine 32(4):531–539. https://doi.org/10.1142/S0192415X0400217X

Sivakumar T, Sambathkumar R, Perumal P, Vamsi MLM, Sivakumar P, Kanagasabai R, Baskaran MV, Subhas SK, Mazumdar UK and Gupta M. 2005. Antitumar and antioxidant activity of *Bryonia laciniosa* against Ehrlich's Ascites Carcinoma bearing Swiss Albino mice. Oriental Pharmacy and Experimental Medicine 5(4):322-330.

Spira A. 1988. The decline of fecundity with age. Maturitas, Suppl 1:15–22. https://doi.org/10.1016/0378-5122(88)90004-7

Sundby J. 1997. Infertility in the Gambia: traditional and modern health care. Patient Education and Counseling 31(1): 29–37. https://doi.org/10.1016/s0738-3991(97)01006-9

Supriya B, Vijayakumar K, Subramanian N and Kumar MD. 2017. Medicinal values of *Putranjiva roxburghii*-a review. International Journal of Current Pharmaceutical Research 9: 24-56.

Templeton A, Morris JK and Parslow W. 1996. Factors that affect outcome of in-vitro fertilisation treatment. Lancet 348: 1402–1406.

The Times of India. 2015. Ruckus in RS over Ramdev's drug promising male child. TNN. 2015.

Themmen APN and Huhtaniemi IT. 2000. Mutations of gonadotropins and gonadotropin receptors: elucidating the physiology and pathophysiology of pituitary-gonadal function. Endocrine Reviews 21(5):551–583. https://doi.org/10.1210/edrv.21.5.0409 chromosome inactivation in women with idiopathic recurrent pregnancy loss. Fertility and Sterility 76(5):908–914. https://doi.org/10.1016/s0015-0282(01)02845-x

van Balen F and Gerrits T. 2001. Quality of infertility care in poor-resource areas and the introduction of new reproductive technologies. Human Reproduction 16(2):215–219. https://doi.org/10.1093/humrep/16.2.215

van Kooij RJ, Looman CW, Habbema JD, Dorland M and Velde ER. 1996. Age-dependent decrease in embryo implantation rate after in vitro fertilization. Fertility and Sterility 66(5):769–775. https://doi.org/10.1016/s0015-0282(16)58634-8

Varier FS. 1995. Indian Medicinal Plants, Vol. 3. Hyderabad, India, Orient Longman 34–37.

Varshney AK, Aquil M, Rahman W, Okigawa M and Kawano N. 1973. Biflovones From *Putranjiva roxburghii*. Phytochemistry 12: 1501-1502.

Velde ER and Pearson PL. 2002. The variability of female reproductive ageing. Human reproduction update 8(2): 141–154. https://doi.org/10.1093/humupd/8.2.141

Ventura SJ. 2001. Vital statistics from the National Center for Health Statistics. In: Data needs for measuring family and fertility change after welfare reform (ed. D. J. Besharov) 21–41.

Wantana R, Tassanee N and Sanan S. 2009. Antinociceptive, antipyretic and anti-inflammatory activities of *Putranjiva roxburghii* Wall. Leaf extract in experimental animals. Journal of Natural Medicines 63(3):290-296.

Warrier PK, Nambiar VPK and Ramanakutty C. 2006. *Indian Medicinal Plants, A compendium of 500 species* Vol.2. Orient Longman. Pp. 342

Wathurkar RN, Chavhan SA and Shinde SA 2019. Phytopharmacognostic Review on *Bryonia laciniosa* (Shivlingi Beej). International Journal of Pharmacognosy and Chinese Medicine. 3(3): 1-7.

CSIR. 2003. *Wealth of India*, 2003. 8. Council of Scientific and Industrial Research (CSIR), New Delhi. Pp. 325-326.

Weinstein M, Wood J and Ming-Cheng C. 1993. Age patterns of fecundability. In: Gray R, Leridon H and Spira A (Ed.), *Biomedical and Demographic Determinants of Reproduction*. Oxford: Clarendon Press. Pp. 209-227.

WHO. 1992. Quality Control Methods for Medicinal Plant Materials. World Health Organization, Geneva.

WHO. 1998. Technical Briefing on Traditional Medicine. Forty-ninth Regional Committee Meeting, Manila, Philippines.

WHO. 2000. General guidelines for methodologies on research and evaluation of traditional medicine. World Health Organization. Pp 41.

WHO. 2003. WHO Guidelines on Good Agricultural and Collection Practices (GACP). World Health Organization, Geneva.

WHO. 2005. WHO Global Atlas of Traditional, Complementary and Alternative Medicine. World Health Organization, Geneva. 1and 2.

Wiersema NJ, Drukker AJ, Mai BT, Giang HN, Nguyen TN and Lamblk CB. 2006. Consequences of infertility in developing countries: results of a questionnaire and interview survey in the South of Vietnam. Journal of Translational Medicine 4:54. https://doi.org/10.1186/1479-5876-4-54

Wood JW. 1989. Fecundity and Natural Fertility in Humans. Oxford Reviews of Reproductive Biology 11: 61–109.

Youngkin EQ and Israel DS. 1996. A review and critique of common herbal alternative therapies. The Nurse Practitioner 21(10). https://doi.org/10.1097/00006205-199610000-00003

Yu Q, Zhang Y, Xia Y, Yang X, Li N, Ye L and Mao X. 2014. Analysis of endothelial nitric oxide synthase (eNOS) G894T polymorphism and semen parameters in a Chinese Han population. Andrologia 46(5):541–546. https://doi.org/10.1111/and.12113

Zhang De-Liang, Zhang Yue-Ting, Yin Jun-Jie and Zhao Bao-Lu. 2004. Oral administration of Crataegus flavonoids protects against ischemia/reperfusion brain damage in gerbils. Journal of Neurochemistry 90(1): 211–219. doi: 10.1111/j.1471-4159.2004.02480.x