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REVIEW ARTICLE

CYNOMORIUM PLANTS: BIOACTIVE COMPOUNDS AND PHARMACOLOGIC ACTIONS

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Summary

Cynomorium coccineum and *Cynomorium songaricum* are unusual parasitic plants in the family *Cynomoriaceae* characterized by their unusual appearance and way of life. Due to their special habit and extremely rare occurrence, in the past, various magical properties have been attributed to these plants. The plant *Cynomorium coccineum*, which is found in the Mediterranean, has been used in Europe since the Middle Ages in folk medicine under the name fungus maletensis (maltese fungus). It was used for the same purpose in Arabic cultures under the name tarthuth. The Asian species (*Cynomorium songaricum*), sometimes considered a subspecies of *C. coccineum*, is still used in traditional Chinese medicine under the name Suo Yang. Recent studies show that the plant has a number of beneficial effects on the body and there is a real possibility that the substances present in Suo Yang or substances derived therefrom will be used in the future for therapeutic purposes. Of particular interest are their effects on sexual function. Preclinical experiments in male rats showed an increase in fertility after administration of *Cynomorium* extract. In these tests, an increase in the weight of the testes and an increase in the number of spermatozoa and their viability were observed. *Cynomorium* plants offer a new approach to the treatment of human infertility, which is currently a major problem.

Key words: Cynomorium; Maltese fungus; traditional medicine; man infertility

Introduction

The use of medicinal plants has accompanied mankind throughout its history. Fragments of some medicinal plants (*Ephedra*, *Althaea*, *Achillea*) were found even in the 60,000-year-old settlements of Neanderthals. Cannabis has been used in China 8,000 years ago and in Mesopotamia, poppy has been used at least 4,500 years ago. The Egyptian Ebers Papyrus, which dates back to 1,550 BC, lists a number of medicinal plants that were used at that time (Tyler, 2000; Samuelsson and Bohlin, 2010). Also nowadays, substances from plants and substances derived from them are of a great importance as medicines for many diseases. Some natural substances may be used directly, others serve as precursors for the production of other semi-synthetic bioactive substances. Also interesting is the possibility of using the known chemical structure of a natural substance as an inspiration in the development of new

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drugs (Shu, 2005; Jones et al., 2006). Many plants have been given magical properties due to their special appearance. Plants that have been attributed an effect on sexual function have been of great interest. *Cynomorium* is one of these plants (Navratilova and Patocka, 2011; Lee et al., 2013; Gu et al., 2018).

Botany

The genus *Cynomorium* L. comprises two species of dicotyledonous parasitic plants with a unique appearance, according to which they were previously described as fungi. The genus was previously classified in the family *Balanophoraceae* (Tutin et al., 1964), but was later assigned to a special family of *Cynomoriaceae* based on morphological features and molecular data (Stevens, 2001). The family *Cynomoriaceae* comprises two species of the genus *Cynomorium* – *Cynomorium coccineum* L. (Fig. 1) and *Cynomorium songaricum* Rupr. (Heywood et al., 2007). *C. songaricum* is sometimes considered a subspecies of *C. coccineum* (Wu et al., 2007; Bellot et al., 2016). Plants are obligatory parasites because they lack chlorophyll. They consist of underground rhizomes with numerous haustoria, which attach to the host plant and draw nutrients from it. The leaves are reduced to scales. The host plants are usually halophytic species on the seashore (e.g. *Atriplex*, *Limonium*, *Tamarix*, *Salsola*, *Obione*, *Nitraria* and some species of the *Cistaceae* family). In spring and summer they grow on the surface of the inflorescence in the form of ears, 15–30 cm tall, consisting of small, densely crowded flowers of reddish-brown to purple-black color. Unlike the *Balanophoraceae* family, in addition to male and female flowers, there are two-flowered flowers in the inflorescence (Weber, Kendzior, 2006; Heywood et al., 2007). The flowers give off a sweet scent and are pollinated by flies (Lebling, 2003). *C. coccineum* grows rarely on rocky coasts in arid areas of Mediterranean and North Africa, *C. songaricum*, also known as Suo Yang, grows in the Middle East and extends to Central and West Asia. This plant is used in medicine, mainly for the treatment of premature ejaculation and impotence. The vast majority of scientific publications on *Cynomorium* plants are devoted to *C. songaricum*.

Figure 1. *Cynomorium coccineum* (Photo: Michal Ducháček)

Ethnobotany

Cynomorium plants have long been used for medicinal purposes. In Europe they were used in the Middle Ages under the name fungus maletensis (Maltese mushroom) according to a well-known site on a rocky cliff near the Maltese island of Gozo (Gebla tal-General, General's Rock, now Fungus Rock). The reef is poorly accessible, about 60 m high and 180 m long (Lebling, 2003) (Fig. 2). The rarity and mystical nature of the plant has led people

Figure 2. Gozo now Fungus Rock, sometimes known as Mushroom Rock, is a small islet in the form of a 60-metre-high massive lump of limestone at the entrance to an almost circular black lagoon in Dwejra, on the coast of Gozo. Photo: Elena Rimeková.

to attribute special power to it. Based on the signature theory, the plant was attributed to a phallic shape to help treat sexual problems. This property, together with its extraordinary rarity, made it highly valued (Attenborough, 1995). Knights of St. John of Jerusalem, they knew the plant already from Jerusalem. When they were forced to leave Jerusalem in the 16th century, they resorted to Malta and found *Cynomorium* on Fungus Rock. He was then closely guarded by soldiers and the thieves awaited severe punishment (sent to galleys and death). In 1651, the Dwejra Tower was built to protect the reef with its growing *Cynomorium*. Knights Hospitaller used dried inflorescences to stop bleeding, prevent infections and to regenerate after combat (Leonti et al., 2020). The plant was also used to treat stomach problems, dysenteria, diarrhoea, hemorrhoids and as an aphrodisiac. Dried inflorescences were sent as a valuable gift to European kings, queens and nobility (Attenborough, 1995; Lebling, 2003; Patocka et al., 2010). Carl von Linné (1755) also mentions the plant. The plant also played a very important role in Arab countries, where it was used under the name *tarthuth*, for example, to treat high pressure, vomiting, colic, stomach ulcers, irregular menstruation, impotence, infertility and venereal diseases. In addition, *Cynomorium* has been used for food, as a spice and as a fabric coloring agent (Lebling, 2003; Nickrent et al., 2005; Heide-Jørgensen, 2008). *C. songaricum* had an important position in traditional Chinese medicine. Under the name *Suo Yang*, it has been used as a tonic and for the treatment of kidney diseases, digestion and impotence (Lebling, 2003; Nickrent et al., 2005; Wu et al., 2007). For medical reasons the interest in recent years seems to have increased again, and measures must be taken to protect it (Heide-Jørgensen, 2008).

Bioactive substances

C. coccineum and *C. songaricum* contain many bioactive compounds (Rosa et al., 2012; Zucca et al., 2016; Sdiri et al., 2018). More than 30 compounds including 8 triterpenoids, 6 flavonoids, 8 phenolic acids, 4 fatty acids, and others have been detected and identified in *Cynomorium coccineum* (Li et al., 2020). A similar situation was also found in *Cynomorium songaricum*. (Cui et al., 2019).

The pharmacologically most important can be considered.

Triterpenoids

Ursolic acid, acetylursolic acid, malonylursolic acid hemiester, ursonazole-12-ene-28-acid-3β malonic acid monoester, oleanolic acid, betulinic acid and triterpenoid saponins have been isolated from *Cynomorium* (Ma et al., 1999; Ma et al., 2009). Triterpenoids of *Cynomorium* could be perspective drugs for treating of cancer (Cheng et al., 2017).

Flavonoids

Many flavonoids are known to have a number of biological activities such as antioxidant, antiinflammatory, antibacterial, antifungal, antiviral and anticancer functions.The main flavonoids in *Cynomorium* are (+)-catechin and (-)-catechin (Hiroki, 1989; Chu et al., 2006; Yu et al., 2010), epicatechin (Tao et al., 1999), (-)-epicatechin-3-O-gallate (Xie et al., 2016), proanthocyanidins (Zhang et al., 2007), citrusin-4-O-glucopyranoside (Cheng et al., 2017), glycosides of citrinin (Qu et al., 2016), epicatechin gallate (Chen and Hatano, 2007) and epiphyllocoumarin (Wang et al., 2015). Other important flavonoids are rutin, quercetin, isoquercetin, isoquercitrin, naringenin, luteolin and phloridzin (Cui et al., 2013; Wang et al., 2015).

Steroids

Cynomorium contains a number of steroids such as β-sitosterol and daucosterol or β-sitosterol oleate (Ma et al., 1993), β-sitosterol palmitate (Chaomei et al., 1999), β-sitosterol-β-D-glucoside (Ma et al., 2002), 5α-stigmasterol-9 and its esters (Qu et al., 1991). Steroids are important bioactive compounds and also play an important role in the pharmacological action of these plants (Xu et al., 1996).

Saccharides, Polysaccharides and other Sugar Derivatives

Glucose (Tao et al., 1999), sucrose (Zhang and Zhang, 1991), ginger oil ketones glucoside (Chaomei et al., 1999), polysaccharides (Zhang and Xue, 1995; Lv et al., 2000) and heteropolysaccharides (Zhang et al., 2001), n-butyl-α-D-fructofuranoside and n-butyl-β-D-fructofuranoside (Sheng et al., 2000; Zhang et al., 2002) were found in *Cynomorium* plants.

Other Substances

From the pharmacologically less important substances, severe proteinogenic and non-proteinogenic amino acids (Fu et al., 1997; Lin et al., 2000), carboxylic acids (Hiroki, 1989; Chen and Hatan, 2007; Qu et al., 2016; Xu et al., 1996; Tao et al., 1999), phenylpropanoids (Cui et al., 2013), lignins (Jiang et al., 2001; Wang and al., 2015), essential oil (Zhou et al., 2009), and condensed tannins (Zhang et al., 1991; Lin et al., 2000; Chang et al., 2005; Zhang et al., 2005) were found in *Cynomorium*. However, as Ben Attia and coworkers (2018) have shown, the chemical composition and antioxidant effects and biological activity of *Cynomorioum coccineum* grown at different sites can vary significantly. Similar situation was found in composition od bioactive substances of *Cynomorium songaricum*. (Cui et al., 2019). In the seven main production areas of China, differences in the chemical composition of bioactive compounds were found and the study revealed that one of the possible factors that may influence the composition of plant secondary metabolites is endophytic fungi (Cui et al., 2019).

Bioactivity

The bioactive substances of *Cynomorium* plants have a number of effects on the body (Meng et al., 2013). Recent studies confirm some empirically acquired knowledge of the use of plants in the past. *C. songaricum* have promising effects against inflammation, aging, fatigue, viruses and cancer and protective effect on the nervous system. This plant also have antifungal effect (Gonçalves et al., 2015), regulates hormones and immune functions (Wang et al., 2016) and also exhibits a neuroprotective and antidepressant effect and improves cognitive functions (Cheng et al., 2017; Miao et al., 2017).

Extract of fresh *C. coccineum* plant has a hypotensive effect, the active ingredient has not been identified (Ikram et al., 1978). *In vitro*, *C. coccineum* extract has an antioxidant potential (Zucca et al., 2013), antiproliferative effects on human cancer lines and antiviral activity against a panel of mammalian viruses (Rosa et al., 2015; Vascellari et al., 2019). *In vivo*, *C. coccineum* treatment prolonged a survival of mice with cancer (Sdiri et al., 2018). Flavonoids have an antioxidant effect and act against fatigue. Experimentally, an increase in the performance of rats in the buoyancy test after administration of *C. songaricum* was confirmed (Yu et al., 2009; 2010). *C. songaricum* ingredients also have an antiviral effect, acting as HIV-1 protease inhibitors (Ma et al., 1999; Nakamura, 2004). *In vitro*, the function of neurotransmitter transporters (GAT-1, DAT, NET, SERT) was affected. *C. songaricum*

extract acts as a DAT/NET activator and GAT-1/SERT inhibitor; increases the dopamine and noradrenaline uptake and decreases the GABA and serotonin uptake (Zhao et al., 2010).

Orally administered *Cynomorium songaricum* extract to ovariectomized rats had a learning and memory enhancing effect in the Morris water maze assay and its effect was probably exerted by p-CREB / BDNF mediated ERK / p38MAPK regulative (Tian et al., 2019). *In vitro*, *Cynomorium songaricum* extracts protect human neuroblastoma cells from β-amyloid and superoxide anion induced injury (Lu et al., 2009). They also prevent damage to nerve and muscle cells during hypoxia, increase superoxide dismutase activity and reduce malonylaldehyde and lactic acid content in nervous cells. They also affect the protein content of muscle cells (Luo et al., 2007). The extract also improves the learning process and memory (Zhao et al., 2002). In perimenopausal rats, *Cynomorium* flavonoids attenuate depressive symptoms (Miao at al., 2017). *C. songaricum* ingredients enhance humoral and nonspecific immunity in mice after cyclophosphamide immunusuppression (Zhang et al., 2008). Very interesting are the effects on the genital system. *Cynomorium songaricum* extract enhances spermatogenesis and expression of GDNF (a factor secreted by Sertoli cells that induces proliferation of undifferentiated spermatogonia). In an experiment in rats, an increase in sperm count and testicular weight was observed when administering the extract (Yang et al., 2010). In another experiment, similar results were obtained after administration of *C. coccineum* and *Withania somnifera* (Abdel-Magied et al., 2001). *Cynomorium coccineum* extract strenghtened the spermatogenesis also in golden hamsters (Lee et al., 2013). Gonadotropin levels and ovarian weight changes were altered in females (Al-Qarawi et al., 2000). The administration of *C. coccineum* extract resulted in an increase in male sperm count and an increase in the proportion of living sperms and their motility (Abdel-Rahman et al., 1999).

A randomized, double-blind, placebo-controlled crossover study of Cappra® for the treatment of mild or mild to moderate erectile dysfunction in Thai male was provided. Cappra® is a herbal medicine which consists of 13 Chinese herbs including *Cynomorium songaricum*. The efficacy was assessed by the International Index of Erectile Function (IIEF) questionnaire and adverse events. There was an improvement of IIEF score for all domains in Cappra® group compared with placebo group. The mean change of IIEF score from baseline for erectile function domain of Cappra® was significantly higher than placebo (4.87 vs. 3.44, $p = 0.032$) (Punyawudho et al., 2012).

A major problem for many developed countries is the steady decline in birth rates, which is due to a number of factors. An important cause is the rise of male infertility, the main cause of which is the inability to produce enough healthy sperm (Krausz, 2011). *Cynomorium* resp. the ingredients of this plant, with their positive effect on spermatogenesis, present a challenge for contemporary medicine, which is not yet very successful in the treatment of male infertility.

Toxicity

Acute toxicity, genetic toxicity and the 90-day repeated oral toxicity of *C. songaricum* (Suo Yang) have been studied in mice (Wei et al., 2019). The acute toxicity test revealed no unusual behavior or increased animal mortality. It has been found that the maximum tolerable dose of this herbal preparation is greater than 15 g/kg. No toxicity effects were observed in three genotoxicity studies. For genotoxicity testing, a bacterial reverse mutation assay, a mouse micronucleus bone marrow assay and a chromosomal spermatocyte aberration assay were used. No increased micronucleus frequencies or structural abnormalities of spermatocyte chromosomes were found in *in vivo* assays. In a 90-day subchronic oral toxicity study in Wistar rats, no haematological changes were observed, nor were any significant toxicological manifestations in the clinical investigation. The NOAEL was 2.83 g/kg of body weight and LOAEL was 5.66 g/kg of body weight (Fu et al., 2019). All of these results suggest that Suo Yang at a given dose is a safe herbal remedy.

Perspectives and Conclusions

Scientific research into new safe and effective drugs has recently rediscovered natural substances as a huge reservoir of innovative therapeutic agents for human health. Relatively recently, several research groups have begun to seek confirmation of the effect of some traditional treatments with natural substances and to study their previously unknown biological activities (Zucca et al., 2019). Recent animal studies show that the substances of *C. coccineum* and *C. songaricum* have a number of interesting effects on the body. Numerous studies have confirmed the empirical

knowledge gained over thousands of years of use of these plants. Further research is therefore perspective and their use in the future can be expected. Abroad, dietary supplements containing plant extracts for the treatment of sexual dysfunctions are on the market. It is not clear how many active substances these preparations contain (if any). Experiments Griffin et al. (2017) provided initial evidence for the direct production of high-quality *Cynomorium* nanoparticles with preserved biological activity. This may be more convenient and much cheaper for the preparation of medicaments than the time-consuming extraction, separation and isolation of individual biologically active compounds. What is certain, however, is the need to develop cultivation techniques for the cultivation of these plants. The cultivation of parasitic plants is problematic, but their excessive collection in the wild threatens to eventually kill of them (Nickrent et al., 2005). Once an extinct species is lost forever (evolution does not repeat), it is important to preserve not only these species for the future.

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Conflict of Interest

The authors declare that there is no conflict of interest with regard to the topic, creation and publication of this article, and no pharmaceutical company has supported the creation or publication of the article.

Adherence to Ethical Standards

This article does not contain any studies involving animals performed by any of the authors.

This article does not contain any studies involving human participants performed by any of the authors.

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