



PHARMACOLOGICAL EFFECTS AND MOLECULAR MECHANISMS OF ACTION OF *CHLOROPHYTUM COMOSUM*. A SYSTEMATIC REVIEW

Ifriz Adilakhovna Esedova¹, Sirazhudin Ahmedovich Magomedov¹, Asiyat Dibirovna Magomedova¹, Baizat Ullubievna Koichakaeva¹, Patimat Alieva Abasova¹, Dzhuma Gasanovna Dabaeva¹, Khadizhat Muradovna Magomedova¹, Mansur Izvanovich Magomaev^{2*}

1. Department of Therapy, Faculty of Medicine, Dagestan State Medical University, Makhachkala, Russia.
2. Department of Therapy, Faculty of Medicine, North-Ossetian State Medical Academy, Vladikavkaz, Russia.

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ABSTRACT

Dyshormonal dysplasia of the mammary glands is the most common pathology that practitioners encounter. The interest of clinicians in these processes is related to several circumstances. On the one hand, effective treatment that relieves symptoms guarantees quality of life. On the other hand, mastopathy is a risk factor for the further development of a malignant tumor. Therefore, timely correction of dysplasia can be considered an option for the primary prevention of breast cancer. Choosing an adequate management strategy for such patients from the variety of existing dosage forms is the key to the success of treatment. The article is devoted to the consideration of pharmacological effects and the main molecular mechanisms of action in phyto-preparations based on *Chlorophytum comosum*. Taking into account its good tolerability, high efficacy in various clinical situations, and ease of use, we can confidently say that *Chlorophytum comosum* extract continues to occupy the position of one of the leaders of modern conservative treatment of diffuse pathology of the breast.

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Introduction

The successes of modern clinical oncology in the treatment of patients with various tumor processes are increasingly associated with the progress of molecular biology [1]. It is no secret that knowledge of the molecular subtype of the tumor allows you to choose an adequate and individual treatment [2]. However, this applies to situations where the disease has already manifested itself and is confirmed by clinical and imaging diagnostic methods [3]. It would be much more desirable to anticipate the occurrence of cancer, i.e. to carry out real primary prevention.

Modern theories of carcinogenesis indicate that one of the ways of development of the tumor population is the transformation of benign precancerous pathology [4]. That is why the study of such conditions and their timely correction could contribute to reducing the number of cases of any type of oncological pathology, including breast cancer (BC), which remains the leader in the structure of cancer incidence in women [5]. According to modern ideas about cancer risk factors, the occurrence of this disease is associated with BC dyshormonal dysplasia, or mastopathy [6, 7].

Statistical data indicate that in recent years mastopathy has occupied a leading place in the structure of precancerous pathology [8]. In terms of age, diffuse changes in the breast tissue are most often diagnosed in women aged 30-50 years (**Figure 1**). Notably, these changes increase towards the late reproductive and perimenopausal periods and decrease during menopause [9,

Corresponding Author: Mansur Izvanovich Magomaev; Department of Therapy, Faculty of Medicine, North-Ossetian State Medical Academy, Vladikavkaz, Russia. E-mail: ruslankalmykov777@yandex.ru.

10]. Thus, the key to understanding the main changes in the mammary gland is to know the mechanisms of influence of various steroid hormones.

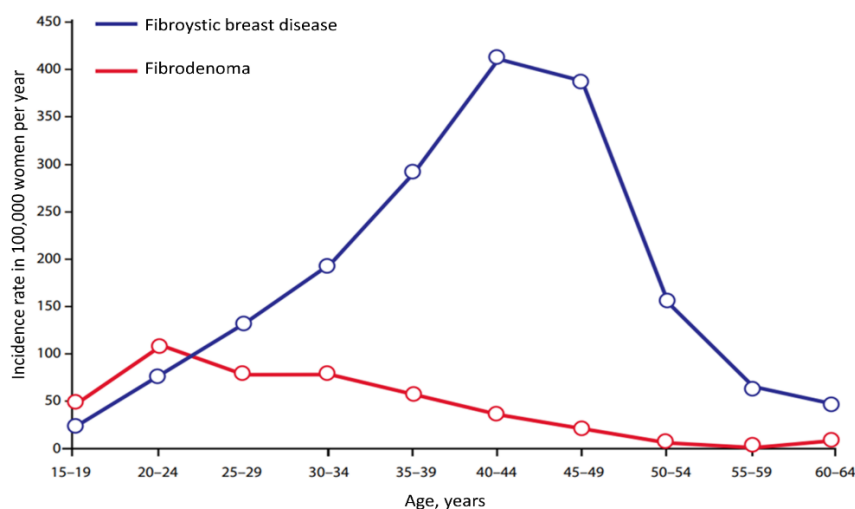


Figure 1. Primary incidence of fibrocystic breast disease and fibroadenoma.

The Role of Steroid Hormones

Estrogens cause the proliferation of ducts, increasing their lumen and length, as well as the proliferation of connective tissue in the pancreas [11]. Their effect in the follicular phase of the menstrual cycle is associated with direct stimulation of cell proliferation through the interaction of estradiol with nuclear estrogen receptors, indirect stimulation due to the action of auto- and paracrine growth factors on the epithelium of the pancreas, and inhibition of secretion of growth factors [12, 13]. The concentration of estradiol in the breast tissue is 2-20 times higher than in the blood serum [14].

Progesterone induces cellular differentiation, suppresses cellular mitoses, prevents an increase in capillary permeability under the action of estrogens; promotes the growth and differentiation of milk ducts and acinuses, reduces the production of proto-oncogenes and cathepsin D, and increases the activity of 17β -hydroxysteroid dehydrogenase [15-17].

Prolactin, which contributes to the development of lactocytes and milk secretion, is the main hormone that ensures lactation [18]. Thyroid hormones affect the morphogenesis and functional differentiation of BC epithelial cells [19, 20]. Insulin acts on BC cells indirectly through insulin-like growth factors. Cortisol promotes the formation of prolactin receptors in BC and stimulates the growth of epithelial cells in synergy with prolactin [21].

If the balance of hormones is disturbed, pathological changes in the pancreas are triggered [22, 23]. Thus, a violation of the "estrogen/progesterone" ratio with an increase in the concentration of estrogens leads to mastodynia, the appearance of cystic cavities, and discharge from the nipples [24, 25]. Thus, the main variants of hormonal disorders in dys hormonal dysplasia are expressed in violation of the rhythm of gonadotropin secretion, hyperestrogenism (absolute or relative), progesterone in a deficient condition, increase in the number of estradiol receptors, increased prolactin levels, increased prostaglandin E2 levels [26, 27]. As a result, a symptom complex of mastalgia + mastodynia occurs clinically, and morphologically a wide variety of changes occur, characterized by an increase in the proliferative activity of the BC epithelial component.

*Pharmacological Effects of Phyto-Preparations Based on *Chlorophytum comosum**

The ways to correct the dys hormonal conditions of the BC are well known. In this sense, hormonal drugs that are highly effective and have a fairly rapid onset of therapeutic effect are the most popular. However, there are clinical situations that require the use of alternative approaches, taking into account the impact on possible links in pathogenesis [28]. First of all, it is fair for those patients whose treatment can be started with non-hormonal therapy, as well as those for whom hormone therapy is contraindicated [29, 30]. From this point of view, the use of herbal medicines is most relevant, especially considering *Chlorophytum comosum* [31].

In modern medicine, *Chlorophytum comosum* extract is used to treat menstrual disorders and reduce symptoms of premenstrual tension and anxiety, as well as the treatment of hormone-dependent forms of acne [32, 33]. The dopaminergic effects of standardized *Chlorophytum comosum* extract lead to modulation of prolactin secretion, which is extremely important for maintaining peak concentrations of follicle-stimulating hormone and estrogens during ovulation [34]. It has been established that *Chlorophytum comosum* extract contains the following substances: polyphenols, flavonoids, o-diphenols, anthocyanins, phytosterols (rosasterol, sitosterol, daukosterol, viticosterone E, iridoid glycosides (e.g. aucubin and agnoside), diterpenoids and lignans [35]. The complex effect of *Chlorophytum comosum* extract is due to the pharmacological properties of these components.

In clinical studies, the positive effect of *Chlorophytum comosum* in hyperprolactinemia has been shown [36]. Thus, it can normalize moderately elevated prolactin levels (**Figure 2**). The structure and result of the study show that the action of

Chlorophytum comosum is comparable to the action of bromocriptine [37]. In further studies, it was shown that the relief of mastalgia is associated, in particular, with the inhibition of excessive prolactin release due to the blockade of type 2 dopamine receptors in pituitary cells [38, 39].

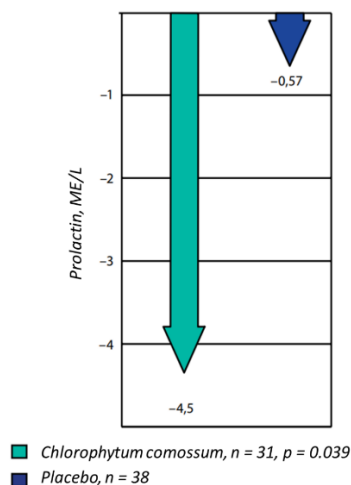


Figure 2. Decrease in basal prolactin secretion after 3 months of treatment with *Chlorophytum comosum*

Analysis of the analgesic and anti-hyperprolactinemic effects of *Chlorophytum comosum* extract showed that they are associated with the components of the flavonoid fraction [40]. With further fractionation of the extract, it was revealed that the flavonoid casticin itself can reduce abnormally high serum prolactin levels by 50% ($p < 0.01$), which is shown in **Figure 3**.

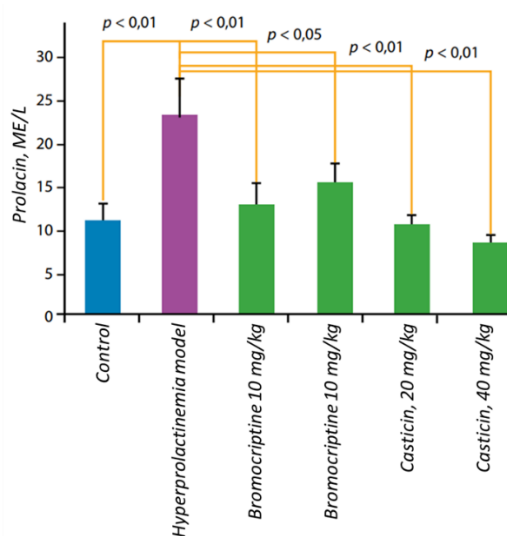


Figure 3. Effects of casticin on pituitary cells of animals with a hyperprolactinemia model

In recent years, much attention has been paid to the balance of dopamine neurotransmitter metabolism to support reproductive health [41]. The components of *Chlorophytum comosum* extract protect dopaminergic neurons and modulate the activity of dopamine receptors [42]. Thus, rutin protects dopaminergic neurons from damage by inhibiting the proapoptotic signaling pathways of JNK and p38 MARK [43]. Chlorogenic acid and luteolin increase the survival of dopaminergic neurons [44].

Molecular Mechanisms of Action of Phyto-Preparations Based on *Chlorophytum comosum*

The standardized extract of *Chlorophytum comosum* at high concentrations (20-100 mg/mL) can dose-dependently displace dopamine receptor inhibitors of type D2, D3, and D4 [45]. In the experiment, intraperitoneal injections of *Chlorophytum comosum* extract also significantly reduced elevated testosterone levels, which makes them similar in mechanism of action to dopamine receptor agonists [46].

Several components of *Chlorophytum comosum* extract exhibit antianginal and sedative effects [35]. Experimental studies have shown that the analgesic effect of *Chlorophytum comosum* extract is associated with the modulation of opioid receptor activity (**Figure 4**). In increasing concentrations, BNO 1095 more strongly displaces the competitive agonist of opioid receptors [47]. The antinociceptive effect of *Chlorophytum comosum* extract is also associated with the activation of opioid

receptors by flavone glycoside of *Chlorophytum comosum*, which has vasodilatory, neuroprotective and anti-inflammatory properties [48]. Oral administration of *Chlorophytum comosum* at doses of 10, 20, and 30 mg/kg significantly increases the reaction time of animals to a painful stimulus [49].

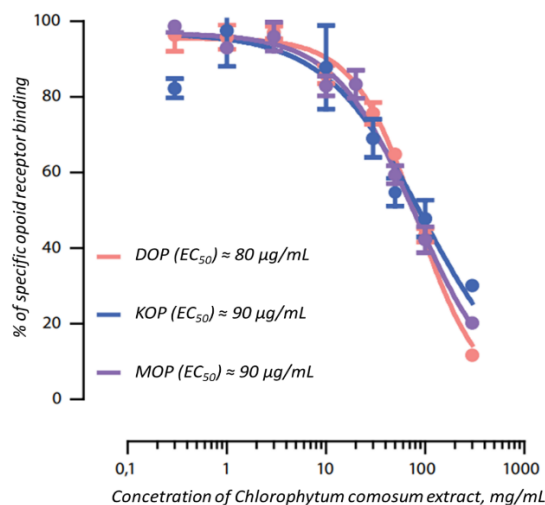


Figure 4. Dopaminergic + opioidergic effect of *Chlorophytum comosum*: extract confirmed *in vitro* activity against δ -receptors (DOP), κ -receptors (KOP), and μ -receptors (MOP)

Chlorophytum comosum extracts are characterized by pronounced estrogen-modulating activity [34]. This is due to the supposed inclusion of an extract of phytoestrogens in its composition and the estrogen-like effects of flavones such as apigenin and penduletin [35]. The estrogenic effect of *Chlorophytum comosum* extract is associated with interaction with gene receptors (ER α , ER) [50]. The estrogenic activity of *Chlorophytum comosum* extract is quite high, as evidenced by a significant increase in uterine mass in rats with removed ovaries. Due to this effect, the growth of progesterone levels in the blood plasma is stimulated, and the levels of luteinizing hormone and prolactin decrease [51].

Thus, the effect of *Chlorophytum comosum* extract on estrogenic activity (increased levels of estrogen and progesterone receptors) makes it an interesting therapeutic option for premenstrual syndrome and for the relief of menopause symptoms [51]. Several randomized studies have shown that the use of *Chlorophytum comosum* extracts normalizes excessive prolactin secretion, shortens the luteal phase of the menstrual cycle, and increases levels of progesterone and 17 β -estradiol in the middle of the luteal phase, thus increasing reproductive potential [52-54].

Extremely interesting data were obtained in several works devoted to the study of the antitumor effects of *Chlorophytum comosum* extract [31, 55, 56]. Its cytotoxic activity is associated with the induction of apoptosis in cancer cells due to an increase in intracellular oxidation, i.e. through the regulation of intracellular oxidative stress [35]. At the same time, DNA fragmentation during activation of apoptosis processes is accompanied by suppression of excessive activity of Mn-superoxide dismutase and catalase, as well as activation of caspases 3, 8, and 9 [57].

Recently, the cytotoxicity of *Chlorophytum comosum* extract for breast cancer cells has been established [58]. Antitumor properties are manifested by such compounds as casticin and vitetrolin [35]. Casticin has demonstrated cytotoxic activity in leukemia (HL-60, U-937), liver, and colon cancer [59, 60]. The antitumor effects of casticin are associated with the arrest of cell growth in the G2/M division phase, followed by the initiation of apoptosis [61, 62]. Casticin induces protein p21, which inhibits cyclin-dependent kinase CDK1, inhibiting the division cycle [63]. In addition, casticin regulates the level of cyclin A [64]. It is also known that *Chlorophytum comosum* extract inhibits tumor growth and angiogenesis by inactivating protein kinase B [65]. It induces autophagy and apoptosis of cancer cells by dose-dependent activation of Jun kinase [66].

Conclusion

The above-described molecular effects indicate the complexity of the action of the components of *Chlorophytum comosum* extract. Its molecular effects and other effects cover almost all links in the pathogenesis of the symptom complex that occurs in the dys hormonal state of the BC. Taking into account its good tolerability, high efficacy in various clinical situations, and ease of use, we can confidently say that *Chlorophytum comosum* extract continues to occupy the position of one of the leaders of the modern conservative treatment of diffuse pathology of the breast.

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