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A COMPREHENSIVE REVIEW OF ANTIDIABETIC ACTIVITY OF MALVACEAE FAMILY PLANTS

Actuality. Recently, phytoproducts have gained major recognition as effective components in the complex treatment of chronic metabolic diseases, particularly diabetes mellitus. Plants from the Malvaceae family are a potential source of biologically active

compounds that was traditionally have been used in ethnomedicine in different countries for the correction of hypoglycemic states. A fundamental study of the antidiabetic properties of extracts from Malvaceae suggested their perspective for the pharmaceutical development of latest therapeutic and preventive drugs, including nanopharmaceutical products, which can be applied into modern medical practice.

The aim of the study was to analyze the scientific data on the antidiabetic properties of plants of the Malvaceae family and to evaluate their potential as a perspective raw source materials for phytotherapeutic agents in the treatment of diabetes mellitus.

Material and methods to review of the scientific literature, including experimental and review articles, highlights the antidiabetic activity of the studied plants of each Malvaceae subfamily with a focus on their pharmacological properties and therapeutic potential for the diabetes mellitus.

Research results. The results of a comprehensive analysis of scientific literature sources indicate that biologically active extracts and nanoparticles obtained from the representatives of the Malvaceae family showed noticeable antidiabetic and hypoglycemic activity. The pharmacological action of these compounds is often attributed to the presence of polyphenols, particularly quercetin, gallic acid, catechins, and other biologically active metabolites. The key mechanism of implementation of the antiglycemic effect is inhibition of the enzymes α -amylase, α -glucosidase, which regulate the modulation of carbohydrate metabolism and also prevent the excessive release of reducing sugars, which ensures stabilization of the glycemic profile.

Conclusion. The relevance of further studies on pharmacokinetic parameters, molecular targets and safety of extracts and nanoformulation of plants of the Malvaceae in the treatment of diabetes mellitus. In particular, a perspective direction is the development of standardized phytocomplexes based on biologically active metabolites that provide prolonged glycemic action with minimal risk of side effects. Thus, the results of the analysis of scientific sources imply the significant therapeutic potential of representative of the Malvaceae in the phytotherapy for the diabetes mellitus, which reveals new opportunities for the creation of effective and safe herbal medicines with proven mechanisms of action.

Key words: malvaceae, herbal medicines, antidiabetic activity, biologically active compounds, nanoparticles.

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КОМПЛЕКСНИЙ ОГЛЯД АНТИДІАБЕТИЧНОЇ ДІЇ РОСЛИН РОДИНИ MALVACEAE

Актуальність. Останнім часом фітотерапевтичні засоби привертають багато уваги як ефективний компонент у комплексному лікуванні хронічних метаболічних захворювань, зокрема цукрового діабету. Рослини родини Malvaceae є перспективним джерелом біологічно активних сполук, які традиційно застосовувалися в етномедицині різних країн для корекції гіперглікемічних станів. Грунтовні дослідження антидіабетичних властивостей екстрактів рослин родини Malvaceae свідчать про перспективу їх застосування для розроблення нових лікувально-профілактичних засобів, зокрема й нанофармацевтичних препаратів, які можуть бути застосовані в сучасній медичній практиці.

Мета дослідження. полягає у проведенні аналізу наукових даних щодо антидіабетичних властивостей рослин родини Malvaceae і оцінюванні їхнього потенціалу як перспективних сировинних джерел для фітотерапевтичних засобів у терапії цукрового діабету.

Матеріал і методи. Огляд наукової літератури, зокрема її експериментальних і оглядових статей, що висвітлюють антидіабетичну активність відомих рослин, які належать до різних субродин родини Malvaceae, з акцентом на їхні фармакологічні властивості та терапевтичний потенціал у лікуванні цукрового діабету.

Результати дослідження. Результати комплексного аналізу літературних джерел засвідчують, що біологічно активні екстракти та наночастинки, отримані із представників родини Malvaceae, демонструють виражену протидіабетичну та гіпоглікемічну активність. Фармакологічна дія цих сполук переважно зумовлена наявністю поліфенольних компонентів, зокрема кверцетину, галової кислоти, катехінів та інших біологічно активних метаболітів. Ключовими механізмами реалізації антигіпоглікемічного ефекту є інгібування ферментів а-амілази і а-глюкозидаз, що сприяє регуляції вуглеводного метаболізму, а також запобігання надмірному вивільненню редукуючих цукрів, що забезпечує стабілізацію гілкемічного профілю.

Висновок. Актуальними є подальші дослідження фармакокінетичних параметрів, молекулярних мішеней і безпечності застосування екстрактів, нанопрепаратів рослин Malvaceae у терапії цукрового діабету. Зокрема, перспективним напрямом є розроблення стандартизованих фітocomплексів на основі біологічно активних метаболітів, які забезпечують продовжену гіпоглікемічну дію, з мінімальним ризиком побічних ефектів. Отже, результати аналізу наукових джерел вказують на значний терапевтичний потенціал представників родини Malvaceae у фітотерапії цукрового діабету, що відкриває нові можливості для створення ефективних і безпечних фітопрепаратів із доведеними механізмами дії.

Ключові слова: Malvaceae, фітозасоби, антидіабетична активність, біологічно активні речовини, наночастинки.

Introduction. Actuality. Diabetes mellitus is one of the fastest-growing diseases in the worldwide. The International diabetes federation estimates 1 286 cases of diabetes were registered in Ukraine in 2000, and this number is projected to increase to 1 196 thousand cases in 2011 and 2 325 cases in 2021 in 1 000s people (Ukrainian Diabetes Report 2000–2045). Globally, 200 million people lived with diabetes in 1990, and this number is expected to increase to 830 million by 2022 (World Health Organization). Diabetes is often linked to cardiovascular diseases and cancer and is associated with infection complications, such as Covid-19, that makes it more lethal (Tomic et al., 2022).

Plants are an abundant and affordable source of bioactive substances with significant potential for use in pharmaceutical products. This is particularly beneficial in developing countries, where access to synthetic medications is limited. (Przeor, 2022). Compared to chemical antidiabetic compounds, such as metformin, sulfonylureas, which have several side effects, plants tend to have fewer side effects. Plants are considered safe, effective, and may offer alternative mechanisms of action, which associated with multiple reaction between phytocompounds and cells proteins, for developing new medicinal products (ДРЛЗ; Ansaria et al., 2022).

Plants of the Malvaceae family (Mallows) are known to contain biologically active compounds such as carotenoids, phenolic acids, flavonoids, coumarins, alkaloids, polysaccharides that possess antidiabetic properties (Erkainure et al., 2019; Akhtar et al., 2022). Mallows are a diverse and economically important family, distributed in tropical and temperate climates in both hemispheres. The most well-known plants of this family are *Hibiscus sabdariffa* (roselle), *Malva sylvestris* L. (common mallow), *Althea rosea* (marshmallow), *Theobroma cacao* L. (cocoa tree), *Tilia* sp. (linden), *Gossypium* sp. (cotton), etc (Cvetković et al., 2021).

Some plants of the Malvaceae family are recognized as a medicinal plants and are included in pharmacopeias. For example, the Ukrainian pharmacopeia includes 9 monographs for 6 plants of the Malvaceae family, while British pharmacopeia – 10 monographs for 7 plants (ДФУ; BP; Samen et al., 2024).

The objective of this study – to conduct a comprehensive review of the literature regarding the antidiabetic properties of plants belonging to the Malvaceae family. Additionally, the investigation aimed to highlight the therapeutic benefits and possible application of these compounds in the treatment of this chronic disease.

Materials and methods. The literature analysis was analyzed from various academic sources, such as MDPI, Google Scholar, IntechOpen, Springer databases. The following keywords were used for the search: “Plant with antidiabetic properties”, “Malvoideae with antidiabetic properties”, “Malvaceae family plants nanoparticles with antidiabetic properties”.

Research results. The Malvaceae consist of over 4225 accepted species, and divided at 10 subfamilies: Grewioideae, Kydia, Byttnerioideae, Helicteroideae, Sterculioideae, Brownlowioideae, Dombeyoideae, Tilioideae, Bombacoideae, Malvoideae (Cvetković et al., 2021). From each of the Malvaceae subfamilies, several plants were selected by deliberate selection to contain all relevant research articles about biological activity and traditional applications in the context of diabetes mellitus and shown in fig 1.

Grewioideae. *Grewia lasiodiscus* leaves ethanolic extract has been shown to prevent glucose uptake by *Saccharomyces cerevisiae*. In an initial glucose solution (1 mg/ml), uptake was inhibited by 50%, whereas at 5 mg/ml, uptake reached to 75%. This adsorption is linked with tannins and flavonoids (Elosh et al., 2024).

Similarly, fruit extracts of *Grewia asiatica L.* (phalsa) were tested *in vivo* on rats with induced diabetes: glucose level in the control group averaged 175,0 ml/dl, while animals with diabetes had 395,15 ml/dl. The glucose level in the group that was treated with extract decreased to 115,0 ml/dl (Akram et al., 2021).

The 80% ethanolic leaf extract of *Cochchorus olitorius L.* (nalta jute) was studied *in vivo* in rats. The extract was found to lowered the level of glucose in the blood and regenerate β-cells (Olysanya et al., 2018).

The methanol-macerated and freeze-dried fruit extract of *Desplatsia deweurei* exhibited antiglycemic activity on days 7, and 14 that was higher than glibenclamide (Idu et al., 2024).

Kydia. The powdered bark of Kydia calycina combined with other herbs, for example, *Bombax ceiba* (also belonging to the Malvaceae), has been shown to decrease blood glucose levels. However, it is mechanism of action remains unidentified (Goyal et al., 2020).

Byttnerioideae. *Theobroma cacao L.* (cocoa), *Theobroma grandiflorum* (cupuassu) liquors have been shown to increase the body and liver weights of diabetic rats and lower glucose levels. Over 40 days, the effect of the herbs on triacylglycerol levels in rat blood plasma was measured: the control group (received only water) had 513 ± 139 ml/dl; group cup1 (the animal was feed with 3,6 g/kg water solution of cupuassu liquor) – 286 ± 105 ml/dl; cup 2 (7,2 g/kg of cupuassu liquor) – 267 ± 112 ml/dl; coc 1 (3,6 g/kg water solution of cocoa liquor) – 328 ± 144 ml/dl; coc 2 (7,2 g/kg water solution of cocoa liquor) – 263 ± 122 ml/dl (De Oliveira et al., 2013). The aqueous extract of *Theobroma cacao* husk, considered agricultural waste, has also confirmed *in vitro* antidiabetic properties, which were investigated by an assay with a dialysis membrane and yeast (Cura et al., 2021).

A methanolic extract of the entire plant *Waltheria indica L.*, obtained by the Soxhlet method, decreased the sugar level in the blood, cholesterol and triglyceride content, and had antioxidant activity proven by *in vivo* studies on rats (Kannan et al., 2016).

Helicteroideae. The bioactive compounds of *Durio zibethinus L.* (durian) fruit rinds of the plant chloroform fraction (concentration 1 000 µg/ml) inhibited α-amylase

Grewioideae	<i>Corchorus olitorius L.</i> <i>Desplatsia deweurei</i> <i>Grewia lasiodiscus</i> <i>Grewia asiatica</i>	Dombeyoideae	<i>Pterospermum xylocarpum</i>
Kydia	<i>Kydia calicina</i>	Tilioideae	<i>Tilia americana</i>
Byttnerioideae	<i>Theobroma cacao L.</i> <i>Theobroma grandiflorum</i> <i>Walteria indica L.</i>	Bombacoideae	<i>Adansonia digitata L.</i> <i>Bombax ceiba</i>
Helicteroideae	<i>Durio zibethinus L.</i> <i>Helicteres angustifolia L.</i>	Malvoideae	<i>Abelmoschus esculentus L.</i> <i>Abutilon indicum</i> <i>Althea rosea</i> <i>Brachychiton populneus</i> <i>Gossypium herbaceum</i> <i>Hibiscus articulatus</i> <i>Hibiscus rosa sinensis</i> <i>Hibiscus sabdariffa</i> <i>Malva neglecta</i> <i>Malva parviflora</i> <i>Malva pseudolavatera</i> <i>Malva sylvestris</i> <i>Pavonia odorata</i> <i>Sida cordifolia</i> <i>Thespesia garckeana</i>
Sterculioideae	<i>Abroma augusta</i> <i>Cola nitida</i> <i>Cola acuminata</i> <i>Sterculia villosa</i> <i>Sterculia foetida</i> <i>Sterculia setigera</i>	Brownlowioideae	<i>Brownlowia tera</i>

Fig. 1. Subfamilies of Malvaceae and plants, which was reviewed in this work

Antidiabetic plants of the Malvaceae family

and α -glucosidase enzymes by 83,06, 81,14% respectively, which were lower than acarbose. The studied fraction contained higher levels of flavonoids and quercetin, which help regulate hyperglycemia and prevent oxidant-mediated liver damage by reducing lipid peroxidation (Tran et al., 2023).

The ethanolic extract of roots and explants grown from the leaves of *Helicteres angustifolia* L. exhibits antglycemic, antiradical, and immunomodulatory effects (Hu et al., 2016).

Sterculioideae. *Sterculia villosa* showed concentration-dependent activity against α -amylase and α -glucosidase. The IC_{50} of the methanolic leaf extract inhibits amylase at $87,73 \pm 1,9 \mu\text{g/ml}$, as opposed to $27,77 \pm 1,4 \mu\text{g/ml}$ for the standard medication acarbose. The extract was active even at the lowest concentration. An in silico study identified stigmasterols as the most active antidiabetic structure compared to γ -sitosterol, lupeol, stigmata-3,5-dien (Hajra et al., 2024). Therefore, both *Sterculia foetida* and *Sterculia setigera* have proven antidiabetic effects (Swarnalatha et al., 2019; Abba et al., 2022).

Cola nitida, *Cola acuminata* have been experimentally shown to exhibit hypoglycemic activity in rats. This activity is linked to the contents of caffeine, theobromine, phenols, tannins, saponins, flavonoids, and carotenoids (Erukainure et al., 2019; Victoria et al., 2023).

Abroma augusta, extracted with ethanol, which is rich in abromine (betaine), triterpenoids, alkaloids, triterpenes, flavonoids, megastigmenes, glycosides, has shown antglycemic activity in clinical trials. The clinical trials were conducted at the Homeopathic medical college – Viniyaka mission hospital (Venkatesan et al., 2020).

Brownlowioideae. The ethanolic extract of *Brownlowia tera* leaves reduced the catalytic activity of enzymes associated with diabetes (α -amylase and α -glucosidase), which is attributed to the following biologically active substances: quaracetine, myrecetine and catechol derivatives (Chakrabarty et al., 2020).

Dombeyoideae. The extracts of three species of *Pterospermum xylocarpum* leaves prevented glucose accumulation by the yeast model, with IC_{50} value for methanolic extract – $45,36 \mu\text{g/ml}$ and $81,9 \mu\text{g/ml}$ for water extracts. These results were further confirmed by in vivo studies using on a rat model (Jaber et al., 2018).

Tilioideae. The coumarins and tannins in the ethanolic extract of *Tilia americana* var. *mexicana* (linden) exhibited significant hypoglycemic activity for 4 hours after the rats received the 500 mg/kg extract compared to the control. The antioxidant activity of the extract, estimated by DPPH (EC_{50}), was $8,84 \pm 1,05 \text{ mg/ml}$ (Rodríguez-Magaña et al., 2019).

Bombacoideae. Polyphenolic compounds of *Adansonia digitata* (baobab) extracts inhibit the activity of

digestive enzymes in vitro at various concentrations. The IC_{50} $4,5 \mu\text{g gallic acid equivalent/ml}$ modulates starch digestion by decreasing the activities of alpha-amylase and alpha-glucosidase. Additionally, baobab has a high content of fiber, which can also suppress the release of reducing sugar. *Adansonia digitata* L. fruits increase the number and size of Langerhans islets, regenerating pancreatic cells, which are destroyed by diabetic necrosis and fibrosis. The potential use of baobab for glycemic control has been investigated in various animal models, indicating it is antidiabetic effect in vivo (Silva et al., 2023).

Bombax ceiba is traditionally used to treat diabetes mellitus. The water and water-ethanolic solution (50, 95%) extracts of the plant had high levels of flavonoids and phenols, which inhibited α -amylase, α -glucosidase. The most important active compound identified in this study was determined to be mangiferin, which belong to phenolic compounds, xanthonoid (Katisart et al., 2020).

Malvoideae. The gallic and protocatechuic phenolic acids of *Hibiscus sabdariffa* (roselle) calyxes extracted with ethanol, demonstrated a higher inhibition rate of glycosidase compared to the extract prepared with n-hexane, ethyl acetate, n-butanol in both in vitro and in situ trials. In vivo experiments indicated that the level of rats blood sugar was reduced from $443,64$ to $134,65 \text{ ml/dl}$ after 15 days of oral administration 400 mg/kg of the ethanolic extract (Alegbe et al., 2019).

Similar results were obtained for the ethanolic fraction of *Hibiscus articulatus* leaves, which also lowered blood sugar levels in Wistar rats when administered at doses of 250 and 500 mg/kg (Yakubu et al., 2022).

The ethanol extracts of *Malva sylvestris*, *Malva pseudolavatera* leaves decreased levels of glucose in experimental animals (rats): the positive control had $119,67 \text{ mg/dl}$, the group treated with $1\,000 \text{ mg/kg}$ of *M. sylvestris* – $146,5 \text{ mg/dl}$, $1\,000 \text{ mg/kg}$ of *M. pseudolavatera* – $129,40 \text{ mg/dl}$. *Malva pseudolavatera* has a greater antglycemic effect than *Malva sylvestris* (Sarmiento-Tomalá et al., 2020).

Malva neglecta, contains kaempferol, cinnamic acid, and other phenolic compounds, has scavenging potential, reduces insulin resistance and α -amylase activity, which was observed in *in vitro* and *in vivo* studies on Wistar rats (Akhtar et al., 2022).

Mucilage extracted from *Althea rosea* alleviates the action of hydrolytic enzymes that break down polysaccharides. It has been identified that mucilage contains glycosides, tannins, saponins, steroids. At higher concentration of mucilage ($200 \mu\text{g/ml}$) reduces α -amylase metabolic function to $75 \pm 1,4\%$ and α -glucosidase to $81 \pm 1,2\%$. However, at the lowest concentration ($40 \mu\text{g/ml}$) it inhibits amylase, glucosidase to $35 \pm 1,2$, $44 \pm$

1,5%, respectively. Mucilage helps to control the level of glucose in the blood by water-holding capacity and swelling that intensifies the viscosity of small intestines and blocks glucose diffusion, also by glucose-binding between mucilage and polyphenols (Hassan et al., 2022).

The extract of *Thesperia garckeana*, contains a higher level of luteolin, which recognized for it is potential to inhibits α -amylase, α -glucosidase. This has been demonstrated through *in vitro* results, and in experiments conducted on rats and by molecular docking studies (Alozieuwa et al., 2022).

Ethyl ether and ethanol were used to prepare extracts of *Gossypium herbaceum* (cotton), which has hypoglycemic action toward blood sugar in rats. After 14 days, the ethyl ether extract decreased glucose to 145,56 mg/dl, while the ethanol extract lowered to 133,75 mg/dl. In compassion, the control group of rats with diabetes has 489,16 mg/dl level and those treated with oral drug glibenclamide had level of 130,0 mg/dl. The mechanism of action is linked with increasing secretion from β -cell or accelerating the release of bounded insulin (Velmurugan et al., 2014).

The fruit and seeds of *Abelmoschus esculentus* L. (okra) have been investigated for their antidiabetic investigation. The OMA (okra mucilage extract), OSE (okra seed extract) significantly reduced blood sugar level from 392,66 to 284,83 and 338,16 mg/dl, respectively. Polyphenolic compounds of *Abelmoschus esculentus*, particularly quercetin, can enhance insulin release from pancreatic beta cells. Quercetin has also antioxidant and vasodilator properties. The flavonoids generally regulate glucose homeostasis and insulin activity at the cellular level (Aleissa et al., 2022).

Pavonia odorata Willd. roots have a high level of essential oils, which have antiglycemic effects and toxicity. Chloroform, ethanol extract at 100 and 200 mg/

kg concentration exhibited a maximal effect on lowering blood glucose levels after 10 days (Rayar et al., 2015).

The dosages of 200, 400 mg/kg of aqueous and ethanol extract of whole *Sida cordifolia* plant reduced hyperglycemia in rats with alloxan-induced diabetes, as level of serum triglyceride, cholesterol, etc (Rao et al., 2020).

Plant-based antidiabetic formulation. However, herbal mixtures often have low solubility in water, inadequate absorption, limited permeability. Additionally, the bioactive compounds of plants have rapid degradation and became instable in varying gastrointestinal tracts or under different environmental conditions. Moreover, managing chronic condition such as diabetes mellitus requires to use of large quantities of phytocompounds; however, the toxicity of these products is not yet fully discovered. Another concerns are the potential interaction between compounds within herbal mixtures (Kambale et al., 2022).

To solve the issue of bioavailability for the herbal extract, various types of nanoparticles have been developed. Therefore, we will describe some examples of nanoparticles with antidiabetic properties, that have been biosynthesized using water extract of the *Malvaceae* family plants, and summarize them in the able. This data specifies the importance of exploring plants from the *Malvaceae* family, for medicine to deal with diabetes mellitus and other diseases.

Conclusions. *Malvaceae* is a family of various plant species, that have antidiabetic activity. Leaves, fruit and herb extract possess antidiabetic activity by blocking of the enzymes (α -amylase, α -glucosidase) or by minimizing the adsorption of sugar by the digestive system. Several groups of bioactive compounds with hypoglycemic action have been identified: flavonoids, phenols, essential oils, tannins, etc. Nanoparticles synthesized with Mallows plant extract have antidiabetic activity, are made from various materials, such as metals and polymers, and were tested in *in vitro* and *in vivo* essays.

Table Nanoparticles with antidiabetic activity that synthesized with aim of *Malvaceae* family plant extract

Plant	Part of plant	Nanocarrier	Size of nanoparticles	Antidiabetic activity essay that was used	
				Inhibition of α -amylase	Influence on glucose levels in rats
<i>Sida cordifolia</i> (Alam et al., 2023)	Aerial part	Chitosan	10–30	+	
<i>Malva parviflora</i> (Mohammed et al., 2022)	Leaves	Emulsion	7–20		+
<i>Brachychiton populneus</i> (Naveed et al., 2022)	Leaves	Silver	15		
<i>Hibiscus sabdariffa</i> (Bala et al., 2014)	Leaves	Zinc oxide	12–46		+
<i>Abutilon indicum</i> (Eswari et al., 2022)	Leaves	Zinc oxide	22	+	
<i>Hibiscus rosa sinensis</i> (Kainat et al., 2021)	Leaves	Cobalt oxide	19.98	+	
		Magnesium oxide	22,72	+	

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