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# Plant antidepressants in selected species from the family Fabaceae – a review

Roślinne antydepresanty u wybranych gatunków z rodziny Fabaceae – przegląd

**Summary.** Depression is a serious social problem increasing globally. As specified by the World Health Organization (WHO), this common recurrent condition associated with mood disorders is the fourth most prevalent health problem in the world. Depression has been estimated to affect approximately 10% of the population. With its tendency to recur, the disease affects humans of all ages, regardless of their sex, ethnicity or health. It impedes or totally prevents normal functioning and is often a cause of disability. Many people suffering from depression are afraid to seek help from specialists for fear of being rejected by society or in the belief that this personal weakness can be overcome by themselves. Based on the available literature data, information about compounds with antidepressant activity contained in selected species from the family Fabaceae was collected with special emphasis on their location in the plant organs and on the postulated mechanisms of action.

**Key words**: Fabaceae, depression, biologically active compounds, phytotherapy, neurotransmitters

## INTRODUCTION

Depression is a serious growing social problem and a disorder affecting the mood, behaviour, and mental health. Currently, over 300 million people suffer from depression worldwide [WHO 2017]. This condition can be caused by e.g. hormonal deregulation, thyroxine deficits, deficiencies of testosterone in males and oestrogen in females [Davis and Tran 2001, Payne 2003, Miller *et al.* 2009], and abnormal neurotransmitter function

[Drevets *et al.* 2008, Thase 2009). Neurotransmitters determine the metal health status, and disorders in secretion thereof have serious consequences for the entire organism. There is a close relationship between the mood and reduced levels of serotonin, noradrenaline, γ-aminobutyric acid (GABA), and dopamine [Dyer *et al.* 2005].

Patients with depression are characterised by a low level of serotonin, i.e. an excitatory neurotransmitter influencing the mental and physical status of the organism. Serotonin ensures a feeling of pleasure. Its deficiency results in apathy, deconcentration, sleep disorders, and depression. Additionally, the deficit of this neurotransmitter causes impulsivity, difficulties in controlling behaviour at danger, and a low pain threshold. In turn, an excess of this compound leads to osteoporosis and may be a cause of impaired appetite [Sullivan *et al.* 2006, Hoogendijk *et al.* 2008]. Another key neurotransmitter in the depression condition is noradrenaline and its derivative adrenaline. These compounds regulate blood circulation, cause mental and physical stimulation, and improve the mood. A low level of noradrenaline is a cause of reduced motivation and depression [Delgado and Moreno 2000, Nutt 2006, 2008]. Another neurotransmitter, dopamine, is involved in emotional and cognitive processes, i.e. the so-called higher mental activity, movement and its coordination, muscle tension, and regulation of hormone secretion [Nutt 2006, Dunlop and Nemeroff 2007]. GABA raises the threshold of cell excitability, reduces anxiety disorders, exerts a relaxing effect, and ensures deep sleep. Additionally, it prevents pain, stabilizes blood pressure, and reduces the risk of muscle cramps [Cryan and Kaupmann 2005, Sequeira *et al.* 2009].

Improper diet, e.g. low levels of omega-3 acids and deficiency of folic acid, vitamin $B_{12}$, zinc, iron, and selenium, can be depression risk factors [Bodnar and Wisner 2005].

Currently, new phytochemicals that will be effective in the prevention and treatment of depression are being sought. Fabaceae is the third largest family of terrestrial plants in terms of the number of taxa [Judd *et al.* 2008, Stevens 2008]. Therefore, taking into account the large number of species, special attention has been paid to the antidepressant compounds contained in plants from this group, which are currently being investigated in various animal models.

The aim of the paper was to present current literature data on biologically active compounds with antidepressant activity contained in different organs of selected species representing the family Fabaceae.

## LITERATURE REVIEW

Research on plant antidepressants is focused on numerous plant species from many taxonomic families. Taxa from the family Fabaceae are widespread around the world. They comprise many medicinal plants with compounds characterised by a wide spectrum of pharmacological activity, including antidepressant properties (tab. 1).

***Albizia julibrissin* Durazz** is a popular herb used in traditional Chinese medicine to treat melancholy and improve the mood [Yu *et al.* 2004]. The bark of this species contains flavone derivatives, unsaturated fatty acids, lignan glycosides, and triterpenoid saponins. These compounds may exert antidepressant effects [Kinjo *et al.* 1992, Jung *et al.* 2003, 2004]. As shown by Kim *et al.* [2007], a 5-HT1A receptor system is involved in the antidepressant activity of the *A. julibrissin* bark extract. Li *et al.* [2003,

2006] demonstrated that petroleum ether and ethyl acetate contained in the extract from flowers of this species had antidepressant activity. In turn Guo *et al.* [2013] claimed that antidepressant effects of silk-tree albizia flowers may be due to the presence of total flavonoids.

***Baptisia tinctoria* L.** is known in Indian folk medicine as a remedy for treatment of depression. Hesperitin contained in the root of the species is responsible for its antidepressant properties [Kumar and Kumar 2017]. The antidepressant effect of this flavonoid is dependent on the interaction with the kappa-opioid receptor [Filho *et al.* 2013] and is modulated by serotonergic 5-HT1A receptors [Souza *et al.* 2013]. Donato *et al.* [2014] have reported that the strong antidepressant effect of hesperitin results from inhibition of the L-arginine-NO-cGMP pathway and an increase in the BDNF levels in the hippocampus.

***Canavalia brasiliensis* Mart., *C. ensiformes* L., *C. siliqua* L.** The seeds of some *Canavalia* species have been used in folk medicine. These organs are a rich source of soluble lectin proteins, which recognise and bind specific glycoprotein oligosaccharides [Jacques *et al.* 2013, Rieger *et al.* 2014]. Lectins from *C. brasiliensis* and *C. ensiformes* seeds bind mannose or glucose [Jacques *et al.* 2013]. The antidepressant action of these compounds is associated with their interactions with serotoninergic (via 5-HT1A and 5-HT2), noradrenergic (via α2-adrenoceptors), and dopaminergic (via D2 receptors) systems [Barauna *et al.* 2006]. Lectins exert an antidepressant effect by modulation of monoaminergic neurotransmitter systems and blockage of hippocampal neurotoxicity induced by glutamate and quinolinic acid [Rieger *et al.* 2014]. Researchers suggest the neuroprotective activity of lectins through modulation of the glutamatergic system. As reported by Jacques *et al.* [2013], the neuroprotective effect of lectins against glutamate neurotoxicity requires oligosaccharide interactions and is dependent on the phosphatidylinositol 3-kinase (PI3K)/Akt pathway. In turn, *C. siliqua* pods contain flavonoids, quercetin glycosides, catechins, gallate, epicatechins, polyphenols of gallic acid and ellagic acid, anthocyanins and ellagitannin (Khatib *et al.* 2010]. As demonstrated by Agrawal *et al.* [2011], polyphenols are involved in the antidepressant activity mediated by dopamine and noradrenaline. Avallone *et al.* [2002] have shown that *C. siliqua* pod extracts can be used as a natural product with anxiolytic, sedative, and chemopreventive effects.

***Clitoria ternatea* Linn.** is widely known in India and is used in Ayurvedic medicine [Parvathi and Ravishankar 2013]. The roots of this species contain alkaloids, glycosides, flavonoids, resins, saponins, phenols, triterpenes, proteins, and carbohydrates [Manalisha and Chandra 2011]. In turn, its aboveground parts contain alkaloids, flavonoids, free amino acids, glycosides, phenols, proteins, reducing sugars, steroids, and tannins [Mukherjee *et al.* 2008, Mathew *et al.* 2009, Kavitha and Premalakshmi 2013]. These compounds have a wide pharmacological spectrum [Mukherjee *et al.* 2008]. The antidepressant properties are provided by flavonoids and tannins, which increase the concentration of neurotransmitters: serotonin, noradrenaline, and dopamine and simultaneously inhibit the activity of monoamine oxidase (MAO). In turn, tannins serve an important antidepressant function as a non-selective MAO inhibitor by increasing the level of norepinephrine and dopamine [Parvathi and Ravishankar 2013]. *C. ternatea* extracts can be used as natural antidepressant agents preventing mood disorders [Jain *et al.* 2003, Parvathi and Ravishankar 2013].

Table 1. Antidepressants in selected species family Fabaceae
Tabela 1. Antydepresanty wybranych gatunków z rodziny Fabaceae

| Species<br>Gatunek | Habit<br>Pokrój | Plant organs<br>Organy roślin | Extract or compound<br>Ekstrakt lub składnik | References<br>Piśmiennictwo |
|---|---|---|---|---|
| *Albizia julibrissin* Durazz | tree<br>drzewo | flower<br>kwiat | water extracts*<br>ekstrakty wodne* | Li *et al.* 2003 |
| | | | the petroleum ether and ethyl acetate fraction from the aqueous and ethanol extracts*<br>frakcje eteru naftowego i octanu etylu z wodnych i etanolowych ekstraktów* | Li *et al.* 2006 |
| | | | total flavonoids**<br>flawonoidy ogółem** | Guo *et al.* 2013 |
| | | stem<br>łodyga | methylene chloride fraction*<br>frakcja chlorku metylenu* | Kim *et al.* 2007 |
| *Baptisia tinctoria* L. | herbaceous perennial<br>wieloletnia roślina zielna | root<br>korzeń | the chloroform, methanol and water extracts; flavone – hesperetin*<br>ekstrakty chloroformowe, metanolowe i wodne; flawon – hesperetyna* | Kumar and Kumar 2017 |
| *Canavalia brasiliensis* Mart. | herbaceous perennial<br>wieloletnia roślina zielna | seeds<br>nasiona | lectins – carbohydrate-binding proteins or glycoproteins*<br>białka lub glikoproteiny wiążące węglowodany* | Barauna *et al.* 2006<br>Rieger *et al.* 2014<br>Jacques *et al.* 2013 |
| *Canavalia ensiformis* L. | perennial<br>bylina | seeds<br>nasiona | lectins – concanavalin*, **<br>lektyny – konkanawalina*, ** | Barauna *et al.* 2006<br>Soares *et al.* 2015 |
| *Ceratonia siliqua* L. | tree<br>drzewo | fruits<br>owoce | polyphenols*<br>polifenole* | Agrawal *et al.* 2011 |
| *Clitoria ternatea* Linn. | herbaceous plant<br>roślina zielna | aerial parts<br>części naziemne | methanolic exract*, **<br>ekstrakt metanolowy*, ** | Jain *et al.* 2003 |
| | | root, aerial parts<br>korzeń, części naziemne | alcoholic extract, methanolic extract*, **<br>ekstrakt alkoholowy, ekstrakt metanolowy*, ** | Mukherjee *et al.* 2008 |
| *Griffonia simplicifolia* Baill. | shrub<br>krzew | seeds<br>nasiona | aminoacid 5-hydroxytryptophan^<br>aminokwas 5-hydroksytryptofan^ | Lemaire and Adosraku 2002 |
| *Glycyrrhiza glabra* L. | perennial<br>bylina | root<br>korzeń | water extract*; saponin – glycyrrhizin<br>wodny ekstrakt*; saponina – glicyryzyna | Dhingra and Sharma 2006 |
| *Glycyrrhiza uralensis* Fisch. | perennial<br>bylina | root<br>korzeń | total flavonoids extract**<br>extrakt flawonoidów** | Fan *et al.* 2012 |

| | | | | |
|---|---|---|---|---|
| *Mimosa pudica* L. | annual or perennial herb roślina zielna jednoroczna lub wieloletnia | leaf liść | aqueous extract*/** wodny ekstrakt*/** | Molina *et al.* 1999 Mbomo *et al.* 2012 Shaikh *et al.* 2016 |
| | | aerial parts części naziemne | metanolic extract* ekstrakt metanolwy* | Sajid *et al.* 2013 |
| *Prosopis cineraria* Linn. | tree drzewo | leaf liść | aqueous extract; saponins, flavonoids, alkaloids, glycosides, tannins and phenolic compounds* wodny ekstrakt; saponiny, flawonoidy, glikozydy, taniny i związki fenolowe* | George *et al.* 2012 |
| *Psoralea corylifolia* L. | perenial bylina | seeds nasiona | total furocoumarin* furanokumaryny ogółem* | Chen *et al.* 2005 Chen *et al.* 2007 |
| | | | furocoumarin – psoralidin*** furanokumaryna – psoralidyna*** | Chen *et al.* 2008 |
| | | | furocoumarin – psoralidin* furanokumaryna – psoralidyna* | Yi *et al.* 2008 |
| | | | furocoumarin – psoralen* furanokumuaryny – psoralen* | Xu *et al.* 2008 |
| *Trigonella foenum graecum* Linn. | herbaceous plant roślina zielna | seeds nasiona | methanolic extract; saponin glycosides and flavonoids* ekstrakt metanolowy; saponiny, glikozydy i flawonoidy* | Pawar *et al.* 2008 |
| | | | aminiacid – 4-hydroxyisoleucine* aminokwas – 4-hydroksyizoleucyna* | Gaur *et al.* 2012 |
| | | | ethanolic extract** ekstrakt etanolowy** | Khursheed *et al.* 2014 |
| *Vicia faba* L. | herbaceous plant roślina zielna | testa ochronna warstwa zewnętrzna nasion roślin kwiatowych | methanolic extract* ekstrakt metanolowy* | Alam *et al.* 2016 |

Biological model: * mice, ** rats (swim or forced swim test, open field test, tail suspension test, locomotor activity test, acute toxicity test, rotarod test, grip strength test), *** human DNA extracted from the immortalized hepatocyte cell line, ^ HPLC method was developed for the direct assay of serotonin precursor, 5-hydroxytrophan, in *Griffonia simplicifolia* seeds without animal and human model.

Model biologiczny: * mysz, ** szczury (test pływania lub test wymuszonego pływania, test otwartego pola, test zawieszenia za ogon, test aktywności lokomotorycznej, test ostrej toksyczności, test bieżni drążkowej – rotarod test, test siły mięśni – test pomiaru siły uchwytu), *** ludzkie DNA ekstrahowane z „nieśmiertelnej" linii komórkowych hepatocytów, ^ metoda HPLC zastosowana do bezpośredniej analizy prekursora serotoniny, 5-hydroksytryptofanu, w nasionach *Griffonia simplicifolia* bez wykorzystania modelu zwierzęcego i ludzkiego.

***Griffonia simplicifolia* Baill.** Another important antidepressant medicinal plant is *Griffonia simplicifolia*, which has been applied in folk medicine to treat certain conditions: depression, anxiety, and insomnia [Kumar *et al.* 2010]. *G. simplicifolia* seeds are a source of 5-hydroxytryptophan (5-HTP) (20,83% of fresh weight), whereas leaves and roots contain serotonin (0,1–0,2%) and lectins, respectively. The 5-HTP amino acid is used for treatment of the effects of serotonin deficiency syndrome [Lemaire and Adosraku 2002]. Extracts containing 50–100 mg of 5-HTP in combination with vitamins or mixed with green tea or yerba mate are used as dietary supplements to support the treatment of depression, suppress excessive appetite, and regulate sleep disorders [Birdsall 1998, Turner *et al.* 2006]. This amino acid can be applied in the phytotherapy of depression and insomnia [Shad and Saeed 2007, Keszthelyi *et al.* 2009].

***Glycyrrhiza glabra* L., *G. uralensis*** Fisch. Roots of *G. glabra* contain glycyrrhizin, glycyrrhizic acid, liquirtin, liquiritigenin, and glabranin [Chowdhury *et al.* 2013]. The pharmacological activity of extracts from this species is associated with the presence of 18β-glycyrrhetinic acid [Obolentseva *et al.* 1999]. This flavonoid has antidepressant, anticonvulsant, and memory-enhancing activity [Ambawade *et al.* 2002, Dhingra *et al.* 2004, Dhingra and Sharma 2006, Muralidhran *et al.* 2009]. Flavonoids extracted from *G. uralensis* (liquirtin, isoliquirtin, and fluoxetin) have antidepressant effects [Fan *et al.* 2012]. They substantially increase the concentration of the major 5-HT and NE neurotransmitters and clearly reduce the 5-HIAA/5-HT ratio in the hippocampus, hypothalamus, and cerebral cortex [Wang *et al.* 2008, Zhao *et al.* 2008]. As indicated by Dhingra and Sharma [2005], the triterpenoid saponin glycoside glycyrrhizin (glycyrrhizic acid ammonium) also exhibits antidepressant properties. This activity is related to enhancement of the norepinephrine and dopamine levels.

***Mimosa pudica* L.** is widely used in folk medicine. In some countries (Mexico and Cameroon), it is used to treat anxiety disorders, insomnia, and depression [Ahmad *et al.* 2012, Mbomo *et al.* 2012, Shaikh *et al.* 2016]. The antidepressant action of aqueous extracts of this species involves positive regulation of dorsal raphe nucleus (DRN) 5-hydroxytryptamine (5-HT) neuronal activity and modulation of the GABA receptor function [Mbomo *et al.* 2012]. *Mimosa pudica* contains the alkaloid myosin, tannins, steroids, flavonoids, triterpenes, and glycosylflavones [Muhammad *et al.* 2016, Shaikh *et al.* 2016]. Sajid *et al.* [2013] claims that etanolic extract of this species shows high antidepressant and antinociceptive activity.

***Prosopis cineraria* Linn.** plants have been used in India, Burma, and Sri Lanka in alleviation of many conditions [Burkart 1976, Ruskin 1980]. Extracts from different organs of the species contain flavonoids, alkaloids, diketones, phenols, amino acids, patulitrin, spicigerin, prosogerin, lipids, β-sitosterol, sugars, and vitamins [Purohit *et al.* 1979, Rhoades 1979]. Aqueous leaf extracts containing saponins, flavonoids, alkaloids, glycosides, tannins and phenolic compounds (flavonoids) are used as adjuvants in the treatment of central nervous system disorders. The antidepressant efficacy of these extracts is comparable to that of drugs applied in the therapy of these diseases [George *et al.* 2012].

***Psoralea corylifolia* L.** seeds have long been used in Chinese medicine as a tonic or aphrodisiac agent and in treatment of various diseases [Chen *et al.* 2005, Xin *et al.* 2010]. The furanocoumarins, mainly psoralen, present in these organs exhibit potent antidepressant properties [Chen *et al.* 2005, 2007, 2008, Yi *et al.* 2008]. The compound was found to elevate the levels of serotonin (5-hydroxytryptamine 5-HT) and

5-hydroxyindoleacetic acid (5-HIAA) and to exert a positive impact on the concentration of dopamine (DA). The antidepressant action of psoralen is associated with monoamine neurotransmitters and the hypothalamic-pituitary-adrenal (HPA) system, which plays a key role in the development and course of depression [Yi *et al.* 2008, Xu *et al.* 2008]. As shown by Chen *et al.* [2005, 2007, 2008], the antidepressant activity of furanocoumarins is mediated via monoamine oxidase (MAO) activity, the hypothalamic-pituitary-adrenal (HPA) axis, and oxidative stress. Additionally, the researchers found that the down-regulation of the corticotropin releasing factor (CRF) gene transcription, particularly by psoralidin, is responsible for the molecular antidepressant mechanism.

***Trigonella foenum graecum* Linn.** is one of the oldest medicinal plants. The seeds of this species contain free amino acids. They are dominated by 4-hydroxyisoleucine (4-HI), which accounts for approximately 80% of the total amino acid content. As reported by Gaur *et al.* [2012], this amino acid has antidepressant activity associated with induction of the serotonin precursor (5-HTP). The antidepressant activity of fenugreek seed extracts was also investigated by Pawar *et al.* [2008], who described that the effect of the application of these extracts was comparable to that exerted by standard tricyclic antidepressant agents. These authors suggest that the potent antidepressant activity of *T. foenum graecum* results from the presence of saponin glycosides and flavonoids in the seeds, which act through interactions with the androgenic, dopaminergic, serotonergic, and GABAergic systems. In turn, Khurseed *et al.* [2014] found that the anti-depressant activity of ethanolic fenugreek seed extracts was associated with inhibition of monoamine oxidase (MAO – A and B) activity. Kumar *et al.* [2013] reported that aqueous--alcohol extracts of the seeds of the species alleviate various symptoms of physical fatigue.

***Vicia faba* L.** – the major species from the family Fabaceae – has been known since ancient times as a valuable source of protein. As demonstrated in the pioneering research conducted by Alam *et al.* [2016], the species is a source of easily accessible natural plant antidepressants. The authors attribute the antidepressant activity of extracts from *V. faba* hulls to inhibition of catecholamine reuptake. However, further research is needed to explain this mechanism of action.

## CONCLUSIONS

Literature data indicate that species from the family Fabaceae have long been known and used in traditional folk medicine to relieve symptoms of many conditions, including melancholy, insomnia, chronic fatigue, and mood disorders. Many biologically active compounds that exhibit antidepressant effects have been identified in different organs of plants from this family (seeds, stems, leaves, flowers). The compounds include e.g. flavones and their derivatives, fatty acids, saponins, glycosides, furanocoumarins, proteins, and free amino acids. Various mechanisms of the antidepressant action of these compounds have been proposed, e.g. interactions with the androgenic, dopaminergic, serotonergic, and GABAergic systems. Given the promising results presented in this review, it is necessary to conduct further experiments to isolate bioactive compounds from different organs of Fabaceae plants and to elucidate the mechanism of their action and potential pharmacological application.

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**Streszczenie.** Depresja jest poważnym, narastającym, globalnym problemem społecznym. Według danych World Health Organization (WHO) to powszechne nawracające schorzenie, związane z zaburzeniami nastroju, jest czwartym problemem zdrowotnym na świecie. Szacuje się, że depresja dotyka około 10% populacji. To wykazujące skłonność do nawrotów schorzenie dotyczy ludzi w różnym wieku, niezależnie od płci, rasy, przynależności etnicznej i sytuacji zdrowotnej. Utrudnia lub też całkowicie uniemożliwia prawidłowe funkcjonowanie, a często jest przyczyną niepełnosprawności. Wielu ludzi chorych na depresję obawia się szukać pomocy u specjalistów z obawy przed odrzuceniem przez społeczeństwo bądź w przekonaniu, że jest to osobista słabość, którą można przezwyciężyć samemu. Na podstawie dostępnych danych literaturowych zebrano informacje dotyczące związków o działaniu antydepresyjnym u wybranych gatunków z rodziny Fabaceae ze zwróceniem szczególnej uwagi na ich lokalizację w poszczególnych organach roślinnych oraz postulowane mechanizmy ich działania.

**Słowa kluczowe:** Fabaceae, depresja, substancje biologicznie czynne, fitoterapia, neuroprzekaźniki

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