Bilobil – clinically confirmed effective and safe *Ginkgo biloba* medicine satisfying the highest quality standards

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Key words
Ginkgo biloba, cognitive performance, neurological symptoms, tinnitus, vertigo, peripheral circulation

Abstract
Ginkgo biloba is a plant that has been investigated extensively. It has many pharmacological actions which result in clinical effects, the most important of which are the effects on cognitive performance, peripheral circulation, tinnitus, vertigo and other subjective neurological symptoms. Seven clinical studies have been performed with Krka's Bilobil, a Ginkgo biloba medicinal product. Three of them were based on a dose of 240 mg per day, and this review refers mostly to these three studies. It has been shown that the daily dose of 240 mg of ginkgo extract in Bilobil capsules is effective in enhancing cognitive performance, improving subjective symptoms such as vertigo and tinnitus, and improving peripheral blood flow. It was also pointed out that regular intake which should be long-lasting is important, though it could also be life-long.

Introduction

Ginkgo biloba products are one of the most popular and widely sold herbal products in the world. Not only due to its appearance, ginkgo is fascinating also because of its many properties that can lead to improved health and quality of life, especially those involving cognitive performance, neurosensory performance and peripheral perfusion.

The first green growth which appeared in Hiroshima after the atomic bomb explosion in 1945 was the sprout of a ginkgo tree, indicating that *Ginkgo biloba* is a tree of extraordinary characteristics. It is a living fossil that can survive also in extreme circumstances. It has been used for centuries in traditional Asian (Japanese and Chinese) medicine. Western researchers could not overlook these facts, and now *Ginkgo biloba* is one of the most investigated plants in the world. By 2014, 3,111 scientific articles concerning *Ginkgo biloba* had been published.[1] It was shown that ginkgo has the following pharmacologic actions: improves the rheological properties of the blood, inhibits the platelet activating factor, improves blood circulation, scavenges toxic oxygen-derived radicals, increases tolerance to hypoxia, especially in brain tissue, reduces capillary permeability, inhibits the age-related decline of muscarinic choline receptors and α_2-adrenergic receptors, and promotes choline uptake in the hippocampus. This is why *Ginkgo biloba* extract enhances cognitive performance such as memory, concentration and intellectual abilities, improves dementia symptoms (including primary degenerative dementia, vascular dementia and mixed form), improves neurosensory disturbances such as vertigo and tinnitus and improves peripheral circulation.[2–5]

It was also shown that ginkgo extract is effective in healthy middle-aged volunteers in tasks that require high demands on self-initiated retrieval of learned material.[6] In another study ginkgo extract

improved working memory and subjective effects such as subjective feelings of cognitive clarity and self-reported improvements in memory and attention in young healthy adults.[7]

Bilobil, produced by Krka, contains a quantified extract of *Gingko biloba*. All procedures from planting to the final product are heavily controlled. This ensures that the medicine is of the highest quality. There are three strengths of Bilobil capsules according to the amount of the ginkgo extract contained: Bilobil 40 mg, Bilobil 80 mg and Bilobil 120 mg. Bilobil 120 mg is a product that allows dosage in the amount of 240 mg per day (the highest dose recommended by ESCOP)[2] in a convenient way – with only two capsules per day. With this dosage regimen better patient compliance can be expected.

Bilobil is a medicine of high-quality standards

The raw material of ginkgo, from which the extract is produced and encapsulated in Bilobil, is grown in different areas: France, Italy, the USA and China. The production of the raw material is carried out in accordance with the documented Good Agricultural Practices, which contain information on the origin of the seed, the cultivation of plants in a manner that provides the highest quality, safety and efficacy of the finished herbal product. With Good Agricultural Practices, sustainable cultivation and harvesting of good-quality medicinal plants is provided, respecting and supporting the preservation of medicinal plants and the environment in general. Equipment, personnel, documentation – from cultivation, collection, harvest to storage – are controlled.
The process of extraction is carried out in Europe, ensuring that extraction is on the level of the highest quality process in line with the Good Manufacturing Practices. The extract of ginkgo is in accordance with the European Pharmacopoeia and has the European Certificate of Suitability from the European Directorate for the Quality of Medicines, which ensures that the strict EU authorities' requirements are fulfilled.

Bilobil is an effective and safe medicine

Throughout the years clinical studies have been performed with all the products from the Bilobil range – seven comprehensive interventional clinical studies overall. The aim of the studies was to monitor the efficacy and safety of Bilobil capsules. We can divide these studies into two groups: those with a 240 mg daily dose of ginkgo extract (Table 1) and other daily doses (Table 2).

In the clinical studies different aspects of cognitive performance were taken into consideration. Thus different methods for efficacy evaluation were used, such as the Mini Mental State Examination (MMSE) scale, Luria and Schulte test and Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-cog scale). Apart from cognitive performance other parameters were also evaluated: peripheral circulation with the ankle-brachial index (ABI), neurological symptoms (among others tinnitus and vertigo), quality of life, asthenia, neurological status and others. Not all studies included all these parameters but all these parameters have been evaluated in clinical studies with Bilobil through the years.

In the seven studies a total of 1,104 patients concluded the treatment. Significant improvements were noted in a majority of the parameters measured. In three out of seven studies a high daily dose of 240 mg was used. In continuation we will focus on these three studies. It was shown that treatment with a high dose (240 mg) of ginkgo extract per day is effective and safe.

Study		No. of patients*	Daily dose 240 mg	Duration	Indications/symptoms analysed	Results
Stefanache 2008	Bilobil 80 mg	197	3 x 80 mg	6 months	Cognitive performance	ADAS-cog: from 27.98 ± 13.77 to 18.32 ± 12.63 points, $p < 0.001$
					Tinnitus	Subjective scale 0–3 points: from 1.34 ± 0.99 to 0.39 ± 0.60, $p < 0.001$
					Vertigo	Subjective scale 0–3 points: from 2.26 ± 0.69 to 0.72 ± 0.62, $p < 0.001$
Stefanache 2011	Bilobil 120 mg	166	2 x 120 mg	6 months	Cognitive performance	MMSE: from 17.75 ± 2.91 to 20.81 ± 3.04, $p < 0.0001$
					Tinnitus	Subjective scale 0–3 points: from 2.00 ± 0.76 to 0.68 ± 0.56, $p < 0.0001$
					Vertigo	Subjective scale 0–3 points: from 2.11 ± 0.65 to 0.58 ± 0.57, $p < 0.0001$
					Mood disturbances, sleep disorders, anxiety	Subjective scale 0–3 points – all three subjective symptoms improved significantly, $p < 0.0001$
					Peripheral circulation	ABI: from 0.80 ± 0.18 to 0.88 ± 0.17, $p < 0.0001$
Mishchenko 2012	Bilobil 120 mg	30	2 x 120 mg	3 months	Cognitive performance	MMSE: from 23.7 ± 0.8 to 26.9 ± 0.5, $p < 0.05$
					Attention and verbal memory	Luria test – direct retention, second retention and delayed retention significantly improved, $p < 0.05$
					Attention and short-term memory	Schulte table: from 49.6 ± 2.9 sec to 38.5 ± 2.8 sec, $p < 0.01$
					Asthenia (asthenic condition)	Asthenic Conditions Scale: from 79.8 ± 4.9 to 59.1 ± 5.1, $p < 0.05$
					Neurological syndromes: - cephalic syndrome - vestibulo-ataxic syndrome - asthenic syndrome	All syndromes improved
					Subjective neurological symptoms (vertigo, tinnitus, headache, etc.)	Subjective scale 0–3 points – symptoms decreased
					Quality of life indexes	Questionnaire – quality of life improved
					Blood flow	Doppler sonography – blood flow increased

Table 1: Summary of Bilobil clinical studies with 240 mg daily dose of ginkgo extract.[8–10]

* Number of patients that concluded the study

Study		No. of patients*	Daily dose	Duration	Indications/symptoms analysed	Results
Pawlak-Osinska, Kazmierczak, 2001	Bilobil 40 mg	120	3 x 40 mg	3 months	Tinnitus	Otoacoustic emissions improved
	Bilobil 40 mg	82	4 x 40 mg	3 months	Vertigo, tinnitus, balance	Most parameters improved
	Bilobil 80 mg	40	2 x 80 mg	3 months	Vertigo, tinnitus	Vertigo improved Tinnitus improved due to lower frequency of spontaneous otoacoustic emissions
	Bilobil 40 mg and Bilobil 80 mg	150	2 x 80 mg (61 patients) 3 x 40 mg (89 patients)	3 months	Vertigo, tinnitus, balance	Dose 160 mg was more effective than the dose 120 mg
Matcau 2004	Bilobil 40 mg	99	3 x 40 mg	3 months	Cognitive performance	ADAS-cog: from 20.27 ± 7.63 to 15.23 ± 7.53 points, $p < 0.001$
					Tinnitus	Subjective scale 0–3 points: from 0.78 ± 0.95 to 0.32 ± 0.62, $p < 0.001$
					Vertigo	Subjective scale 0–3 points: from 1.49 ± 0.88 to 0.46 ± 0.58, $p < 0.001$
Yakhno 2007	Bilobil 80 mg	100	2 x 80 mg	3 months	Cognitive performance	Clock Drawing Test, Mattis Dementia Rating Scale, Associations, Digit Forward and Backward, ADAS-Cog (Words List Recall and Recognition), Digit Symbol, Labyrinth, Number strike – all parameters improved
					Subjective neurological symptoms (vertigo, tinnitus, headache, etc.)	Subjective scale 0–4 points – symptoms decreased
					Motoric activity	Questionnaire – motoric activity improved
Maruta 2009	Bilobil 80 mg	120	2 x 80 mg	3 months	Attention and short-term memory	Schulte table: from 52.4 sec to 41.6 sec, $p < 0.05$
					Attention and verbal memory	Luria test – results improved in all repetitions
					Concentration and work capacity	Kreplin method – coefficient of work capacity increased from 0.63 to 0.87, $p < 0.001$
					Asthenia (asthenic condition)	Asthenic Conditions Scale: from 81.5 ± 5.6 to 63.9 ± 4.8
					Neurological syndromes: - cephalic syndrome - vestibulo-ataxic syndrome - asthenic syndrome	All syndromes improved
					Subjective neurological symptoms (vertigo, tinnitus, headache, etc.)	Subjective scale 0–3 points – symptoms decreased
					Quality of life indexes	Questionnaire – quality of life improved
					Blood flow	Doppler sonography and rheoencephalography – blood flow increased

Table 2: Summary of Bilobil clinical studies with 120 mg and 160 mg daily dose of ginkgo extract.[11–17]

* Number of patients that concluded the study

Bilobil was effective in patients with moderate and severe cognitive impairment[9, 18]

A 6-month study with 166 patients with moderate and severe cognitive impairment was conducted by Stefanache et al. Patients took two capsules of Bilobil 120 mg per day, i.e. 240 mg of ginkgo extract per day. Cognitive performance was measured with the MMSE scale and peripheral circulation with the ABI. Subjective symptoms (tinnitus, vertigo, mood disturbances, sleep disorders and anxiety) were measured subjectively by the patients. Significant improvements in all parameters were noted. Bilobil was well tolerated.

Bilobil improved cognitive performance

Bilobil 120 mg improved cognitive performance such as memory and attention in patients with moderate and severe cognitive impairment (possible score: 0–30). In the beginning of the clinical study the average score was 17.75 points and after the treatment it was 20.81 points on the MMSE scale; the difference of 3.06 points was statistically significant ($p < 0.0001$).

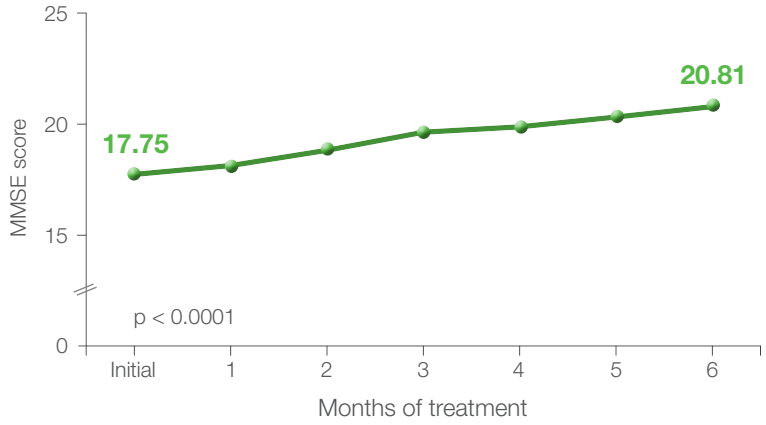

Figure 1. MMSE score before the treatment and after each month of the treatment

Bilobil improved vertigo and tinnitus

Bilobil's efficacy in patients with vertigo and tinnitus was evaluated subjectively, using a 3-point scale (3 meaning severe presence of a symptom and 0 meaning the absence of a symptom). Before the treatment the average score for vertigo was 2.11 and after the treatment the average score was 0.58; the difference of 1.53 points was statistically significant ($p < 0.0001$). Before the treatment 124 patients had moderate or severe vertigo. After the treatment only six of them had moderate

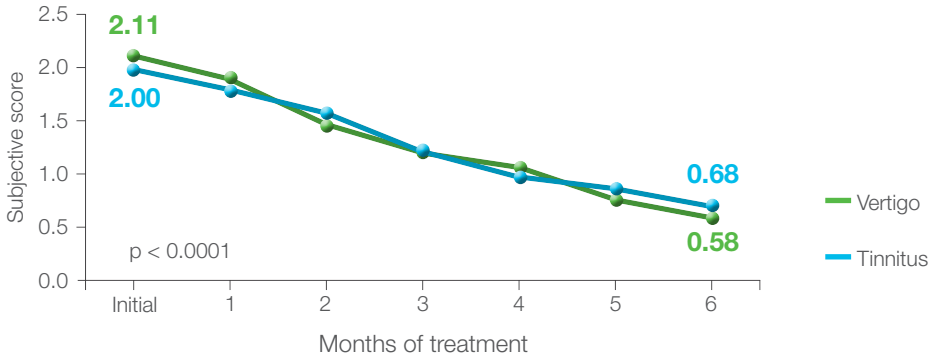

Figure 2. Subjective score of tinnitus and vertigo before the treatment and after each month of the treatment

vertigo but none had severe vertigo. Before the treatment the average score for tinnitus was 2.00 and after the treatment the score was 0.68; the difference of 1.32 points was statistically significant ($p < 0.0001$). Before the treatment 77 patients had moderate or severe tinnitus but after the treatment only 5 patients had moderate tinnitus but none had severe tinnitus.

Bilobil improved mood disturbances, sleep disorders and anxiety

Mood disturbances, sleep disorders and anxiety were also evaluated subjectively, with a 0–3 point scale. Bilobil improved mood disturbances (the average score before the treatment was 1.80, after the treatment it was 0.83; the difference of 0.97 points was statistically significant, $p < 0.0001$); sleep disorders (the average score before the treatment was 1.93, after the treatment it was 0.83; the difference of 1.10 points was statistically significant, $p < 0.0001$) and anxiety (the average score before the treatment was 1.83 and after the treatment it was 0.83; the difference of 1.00 point was statistically significant, $p < 0.0001$).

Figure 3. Subjective score of mood disturbances, sleep disorders and anxiety before the treatment and after each month of the treatment

Bilobil improved peripheral circulation

Bilobil efficacy in symptoms of peripheral circulation insufficiency was monitored by the ABI, which is used to predict the severity of the peripheral arterial disease. Before the treatment the average score was 0.80 and after the treatment it was 0.88; the difference of 0.08 points was statistically significant ($p < 0.0001$). Only the patients with the ABI below 1 at the initial visit were taken into account.

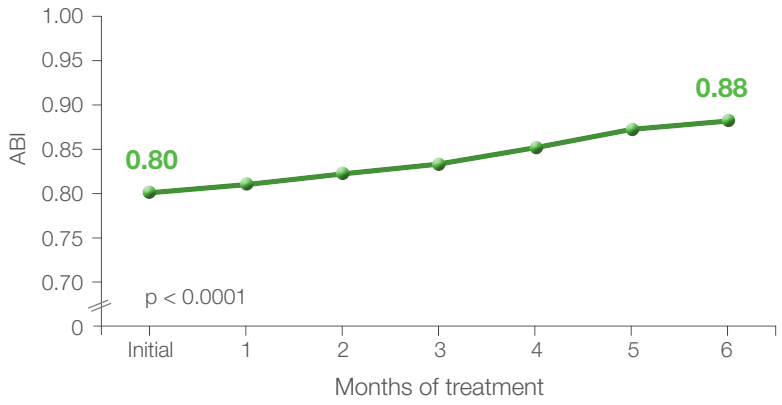

Figure 4. ABI before the treatment and after each month of the treatment

Bilobil improved cognitive performance in patients with severe cognitive impairment[8]

Another 6-month clinical study (Stefanache et al.) was concluded by 197 patients with cognitive impairment. They were treated with Bilobil 80 mg in order to improve cognitive performance such as memory and concentration. Patients took three capsules of Bilobil 80 mg per day, i.e. 240 mg of ginkgo extract daily. Cognitive performance was measured with the ADAS-cog scale, tinnitus and vertigo were measured by means of subjective evaluation. Significant improvements were noted.

Bilobil improved cognitive performance

Bilobil improved cognitive performance such as memory and attention (possible score 0–70). In the beginning of the clinical study the average score was 27.98, after the treatment the average score was 18.32. The difference of 9.66 points was statistically significant ($p < 0.001$).

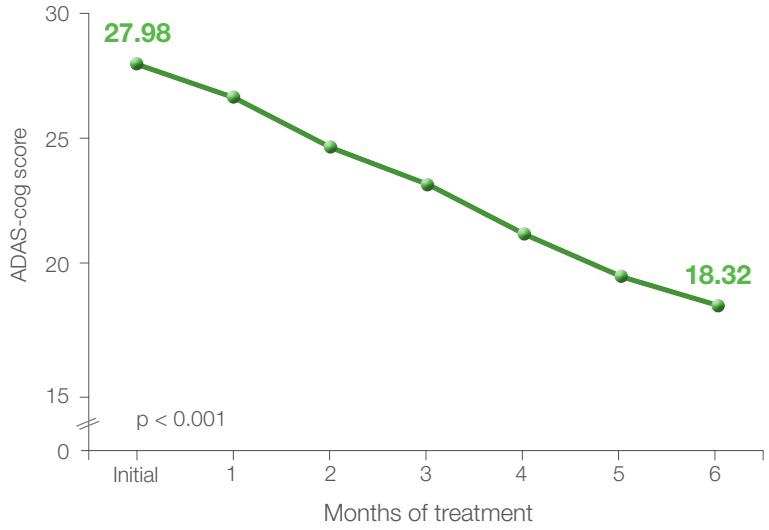

Figure 5. ADAS-cog score before the treatment and after each month of the treatment

Bilobil improved vertigo and tinnitus

Bilobil efficacy in patients with vertigo and tinnitus was evaluated subjectively, using a 3-point scale (3 meaning severe presence of a symptom and 0 meaning the absence of a symptom). Before the treatment the average score for vertigo was 2.26, after the treatment the average score was 0.72; the difference of 1.54 points was also statistically significant ($p < 0.001$). Before the treatment

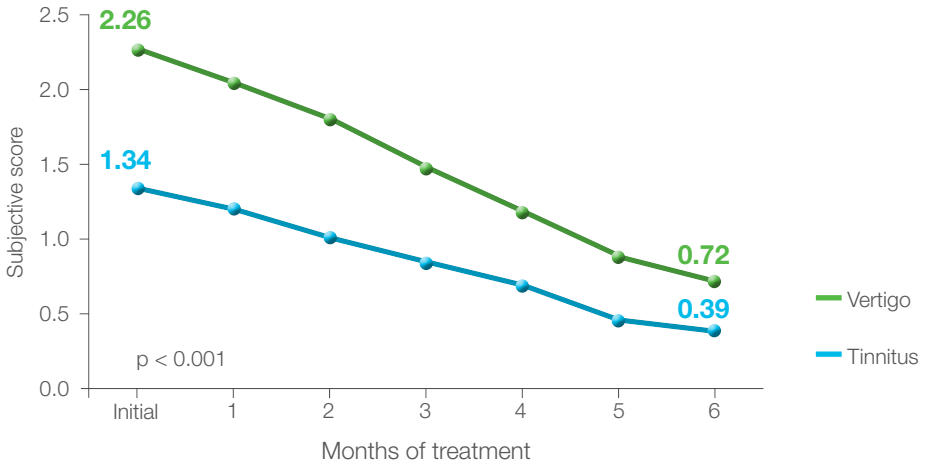

Figure 6. Subjective score of tinnitus and vertigo before the treatment and after each month of the treatment

179 patients had moderate or severe vertigo. After the treatment only 18 of them had moderate vertigo but none had severe vertigo. Before the treatment the average score for tinnitus was 1.34, after the treatment the average score was 0.39; the difference of 0.95 points was statistically significant ($p < 0.001$). Before the treatment there were 94 patients with moderate and severe tinnitus. After the treatment there were only 12 patients with moderate tinnitus but none with severe tinnitus.

Bilobil improved symptoms of cerebrovascular insufficiency[10, 19]

The 3-month study (Mishchenko TS et al.) involved 30 patients with chronic cerebrovascular insufficiency (grade II–III dyscirculatory encephalopathy) of atherosclerotic and/or hypertensive genesis. The patients took two capsules of Bilobil 120 mg per day, i.e. 240 mg of ginkgo extract daily. The following parameters were measured: cognitive performance (with MMSE, Luria test and Schulte table), neurological symptoms (headache, vertigo, tinnitus, unsteady gait, memory disorders, sleep disorders, impaired mood, tearfulness, sensation of fear, impaired performance, anxiety, hot flashes to the head), neurological status, the asthenic condition, quality of life condition, cerebral hemodynamics and laboratory parameters (blood and urine test). It was shown that Bilobil was effective in improving all the listed parameters as demonstrated below.

Bilobil improved neurological symptoms

After the 3-month treatment the number of patients with complaints of neurological symptoms was reduced in all groups of symptoms (headache, vertigo, tinnitus, unsteady gait, memory disorders, impaired performance, impaired mood, sleep disorders, tearfulness, sensation of fear, anxiety, hot flashes to the head).

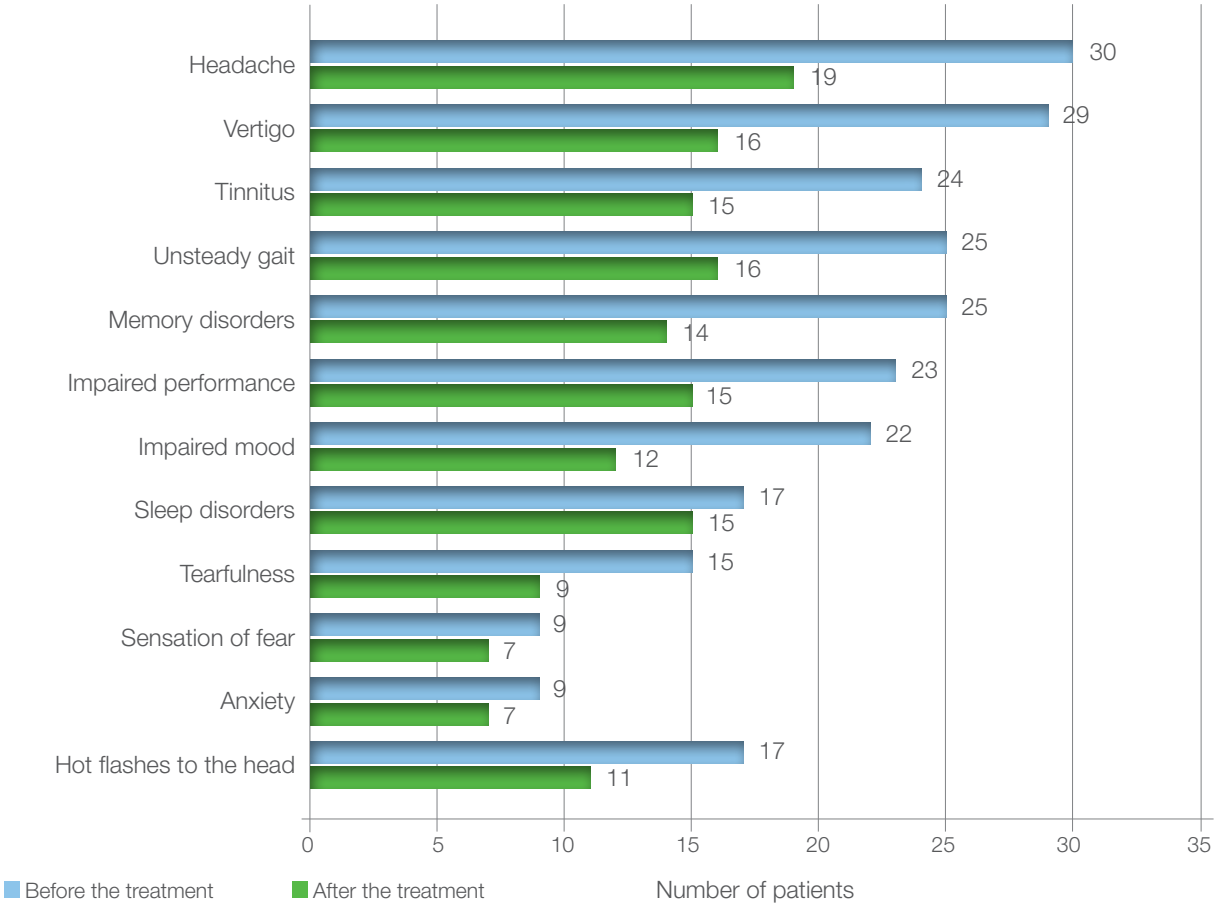

Figure 7. Number of patients with neurological symptoms before and after the treatment

Bilobil improved cognitive performance

Bilobil improved cognitive performance according to the MMSE scale (the maximum score for the general index of cognitive performance is 30). An analysis of cognitive functions showed an improvement in all the indexes.

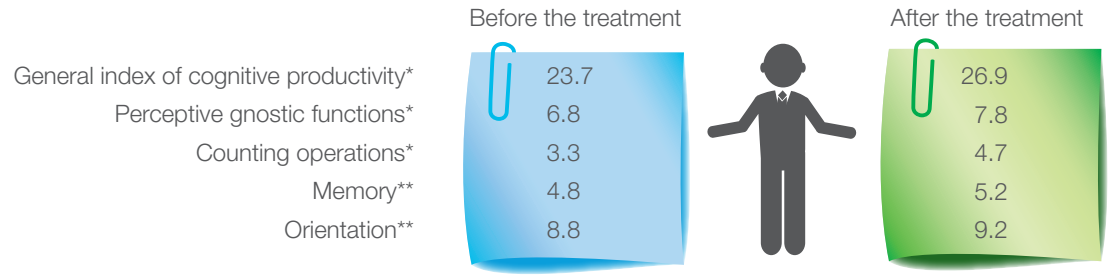

Figure 8. MMSE indexes before and after the treatment (* $p < 0.05$, ** NS)

Bilobil improved short-term memory and attention

The data obtained with Schulte tables allowed us to assess short-term memory and attention in the examined patients. Before the start of the treatment with Bilobil in the daily dose of 240 mg, the average time of test performance was 49.6 seconds. At the end of the study the test results showed a significant ($p < 0.01$) reduction of the time needed to find the figures to 38.5 seconds.

Bilobil improved verbal memory

Verbal memory was measured with the method of memorising ten words with the Luria test. Bilobil increased the number of words remembered and reduced the exhaustion of the patients at the end of the study. The scope of direct retention (average 4.3 words before the treatment and 5.6 after), the scope of second retention (5.5 words before and 6.2 after) and the scope of delayed retention (5.3 words before and 6.1 after) were improved significantly ($p < 0.05$).

Bilobil decreased the number of patients with neurological syndromes

The cephalic syndrome was noted in 100% of the patients before the study, while only 63.3% of the patients demonstrated this syndrome after the 3-month treatment; the vestibulo-ataxic syndrome before the trial was noted in 96.7% of the patients, at the end of the trial it was found in 53.3% of the patients; the asthenic syndrome (neurocirculatory) before the treatment was found in 76.7% of the patients and in 50% of the patients after the treatment.

Bilobil improved the asthenic condition

The average score of the asthenic condition determined with the Asthenic Condition Scale questionnaire before the start of the treatment with Bilobil 120 mg was 79.8 points. The intensity of asthenia after the 3-month treatment was reduced considerably and dropped to 59.1 points on average.

Bilobil improved the quality of life perception

After the treatment with Bilobil 120 mg, life quality indexes based on the questionnaire improved (the maximum was 10 points for each index).

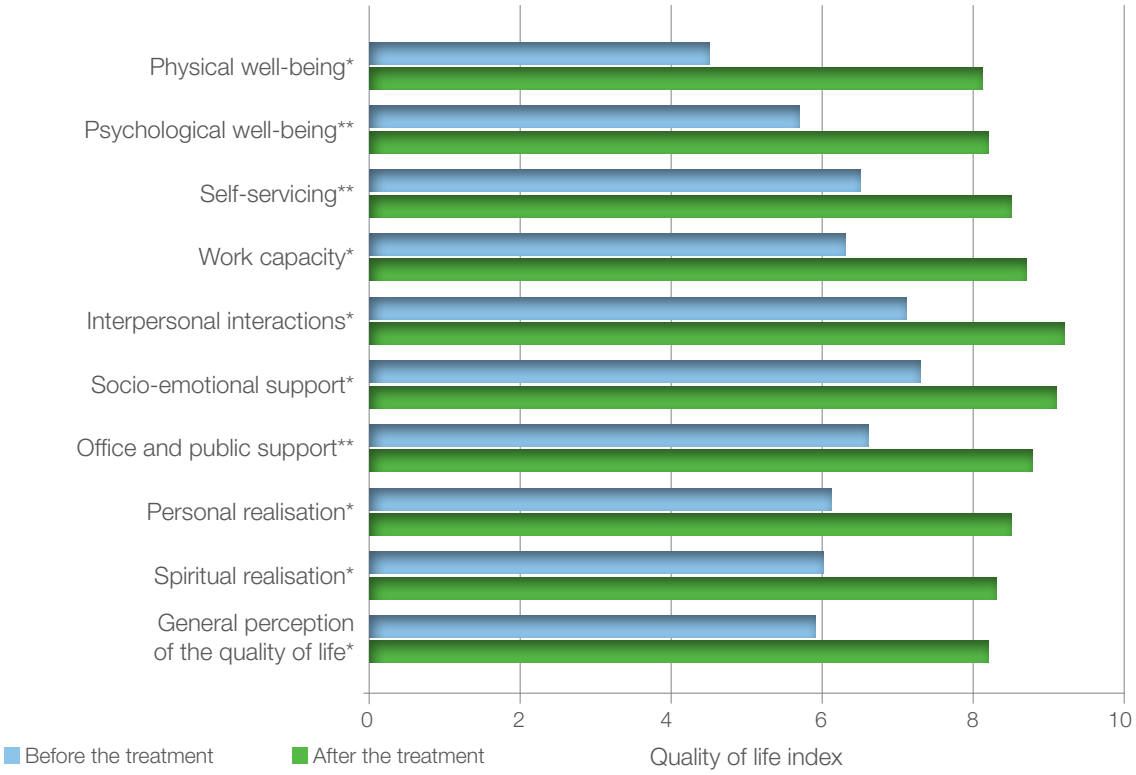

Figure 9. Life quality indexes before and after the treatment (* $p < 0.05$, ** NS)

Bilobil improved cerebral hemodynamics

The treatment with Bilobil in the daily dose of 240 mg led to positive changes in cerebral hemodynamics – the average linear speed of blood flow increased in all vessel systems (*a. carotis communis, a. vertebralis*). No significant changes of heart rate or blood pressure were noted in patients during the study.

Bilobil safety

Bilobil was well tolerated. Most frequent adverse reactions were: headache, insomnia and mild nausea. They were mild and disappeared by themselves. No interruption of treatment was needed.

Conclusions

Clinical studies confirmed the efficacy of Bilobil in the daily dose of 240 mg. Two studies were performed with Bilobil 120 mg (one capsule twice per day) and one was performed with Bilobil 80 mg (one capsule three times per day). All treatment regimens were beneficial for cognitive performance, concomitant subjective symptoms such as tinnitus, vertigo, mood disturbances, sleep disorders, anxiety, headache, impaired performance, sensation of fear, unsteady gait, tearfulness and hot flashes to the head; the perception of the quality of life also improved. Peripheral circulation and cerebral hemodynamics also improved. This conclusion is in line with many other obtainable data from the clinical studies with the ginkgo extract.

In the studies which monitored the 6-month time dependence of the efficacy parameters it was shown that the improvements of these parameters increased each month of the treatment. This allows us to conclude that the daily treatment with Bilobil 240 mg should be long-lasting and could also be life-long.

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Krka in medicine and pharmacy

Published by
Krka, d. d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto, Slovenia

Editor-in-Chief
Breda Barbič-Žagar

Paljk M, Vitezič P, Milharčič Simčič M. Bilobil – clinically confirmed effective and safe Ginkgo biloba medicine satisfying the highest quality standards. Krka Med Farm 2014; 26 (38): 144–154.
Abstract available from: http://cobiss6.izum.si/scripts/cobiss?command=DISPLAY&base=99999&rid=3767665&fmt=11&lani=si

ISSN 0351-6040

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