Middle East Journal of Applied Science & Technology (MEJAST)
Volume 6, Issue 1, Pages 16-37, January-March 2023

Advanced Bioinformatics Tools, coupled and integrated with Manual Techniques, demonstrated the definitive resolution of the plantar deformation, Hallux Valgus, with a long-time outcome of absence of recrudescence

A. Maksimovic[1,*,§,†] & S. Turini[2,3,4,*,§]

Aleksandra Maksimovic [1,*,§,†] - [1]*ALVITA PLUS D.O.O. Nebojsina Ulica/Street 53/7, 11000, Belgrade, Republic of Serbia.*
**Corresponding author Email: info@alvitaplus.rs & [§]Corresponding author Gmail: aleksandruida@gmail.com*

Stefano Turini [2,3,4,*,§] - [2]*Alma Mater Europaea (AMEU-ECM); Slovenska Ulica/Street 17, Maribor, 2000, Slovenia.*
[3]BDORT Center for Functional Supplementation and Integrative Medicine, Kraljice Natalije Street 19, 11000, Belgrade, Republic of Serbia. [4]Unique Treatments doo, Nemanjina 40, 11000, Belgrade, Republic of Serbia.
**Corresponding author Email: turini.stefano@yahoo.it & [§]Corresponding author Gmail: stefanoturini87@gmail.com*

DOI: https://doi.org/10.46431/MEJAST.2023.6103

Article Received: 15 December 2022 *Article Accepted: 27 January 2023* *Article Published: 14 February 2023*

ABSTRACT

Background: Hallux Valgus is a type of plantar deformation that involves an angular deviation of the big toe, inwards, with respect to the long axis of the foot. This creates a state of chronic inflammation with a formation of protusion on articulation of big toe called bunion. As a consequence, people can lose capacity of deambulation and require the contribution of self-propelled supports. The treatment consists of surgery and use of non-steroidal anti-inflammatory drugs. A familiarity in this condition has also recently been highlighted.

Objectives: To demonstrate, how the combined treatment with manual techniques and specific anti-inflammatory, cream is able to resolve plantar deformation without the aid of surgery and without recurrence.

Methods: The synergistic combination of three manual techniques, as: Bowen Technique, Reflexology and Su Jok, coupled with a cream containing Glycerol, Camphor and Povidone Iodine, applied on a cohort of 30 patient, divided in 5 groups, was the basis of the clinical application. In order to confirm the efficacy of the preparation, its composition was compared, by Molecular Docking, with normal antinflammatory drugs.

Results: The results from molecular docking showed a greater affinity, of the components of the cream, than the classical drugs. Furthermore, the statistic of the reduction of the size of bunions, showed a complete success in the reduction of volume of bunion, without recrudescence.

Conclusions: The combined treatment of manual techniques, with the application of a cream, has shown full effectiveness in resolving the Hallux Valgus plantar deformation, without the appearance of recrudescence.

Keywords: *Hallux Valgus; Bowen Technique; Reflexology; Su Jok; Molecular Docking; Camphor; Povidone Iodine.*

Introduction

Background about Hallux Valgus (Bunion)

Hallux Valgus also known as Bunions, or Hallux Abducto Valgus, Metatarsus Primus Varus, are a common forefoot condition characterised by deformity at the great toe metatarsophalangeal joint (MTPJ). The great toe deviates laterally and the metatarsal deviates medially, resulting in a painful prominence at the dorsomedial aspect of the metatarsal head. Australian patients seek general practitioner (GP) treatment for bunions at a rate of 4.2 per 10,000 encounters [1]. Increased prevalence is seen in women and older patients. In the Australian population, 82.3% of patients who present to their GP with bunions as their chief complaint are female, and 80.5% of patients are aged ≥ 45 years [1]. The overall prevalence in the adult population is 23% [2]. Juvenile bunion (paediatric hallux valgus) can be defined by the presence of an open growth plate, and it is rare [3]. The majority of patients are female, and half present before 10 years of age [3]. Bunions are a common foot complaint, and patients may present to their GPs seeking advice or referral to an orthopaedic surgeon.

The aim of this article is to review the non-operative management of bunions, as well as provide a brief overview of operative treatment and indications for referral.

Aetiology

Patients often present with medial forefoot pain and difficulties with shoe wear. Bilateral deformity is common [4]. The most common source of pain is the dorsomedial eminence; however, patients may complain of pain under the lesser toe MTPJs (transfer metatarsalgia) due to the loss of effective weight-bearing through the first ray [4,5]. Patients frequently have associated lesser toe deformities (such as hammer toes) and painful plantar keratosis [5]. Severe deformity can lead to altered gait biomechanics and an increased risk of falls in elderly patients [6]. The natural history of bunions is generally progression of deformity over time, rather than stable symptoms or improvement. Despite many proposed causes, the exact aetiology of hallux valgus is unclear. Many patients have a positive family history for bunions, and there is likely a heritable component [4,7]. While often implicated, a causative relationship between bunions and footwear, particularly high heels, has not been shown in the literature [8]. Pes planus (flat foot) and generalised ligamentous laxity may contribute to juvenile bunions [3]. Treatment should be directed by the patient's main concerns. This may be pain, cosmesis or difficulties with footwear.

Non-Operative Treatment

It is recommended that footwear be accommodative, with a wide, deep toe box and a low heel. Referral to a podiatrist for shoe stretching or modifications may assist patients in wearing their desired footwear, and it is particularly useful for patients with associated peripheral vascular disease or diabetes who may be at increased risk of skin breakdown. Padding over the medial eminence with an over-the-counter bunion cushion may provide symptomatic relief. There is some evidence to support orthotics, toe spacers, splinting and braces, which may provide symptomatic relief and decrease pain in some patients [9–13]. Unfortunately, the available literature on the use of orthotics is limited, and no strong conclusions can be drawn regarding their use. If they do lead to improvement in symptoms, this effect is unlikely to last long term [9]. It is also important to note that correction of the deformity will not occur with braces or splinting [12,13]. For patients who complain of transfer metatarsalgia, a metatarsal dome may help offload the lesser toe metatarsal heads. Orthotics to address associated pes planus in paediatric patients may also relieve bunion pain [3]. Anti-inflammatory medications are recommended for pain relief [14]. However, given the increased prevalence of bunions with increasing age, comorbidities such as renal impairment and peptic ulcer disease may preclude their safe use. Opioid medication should be avoided wherever possible. It is important to note that non-operative management may not be successful in all patients. While there have been individual studies showing symptomatic relief with non-operative management, a Cochrane review published in 2004 found no difference when compared with no treatment at all [15]. A trial of non-operative management is still advised, and may be of particular use for adolescent patients, those awaiting orthopaedic review and patients unfit for, or not desiring, surgery. As non-operative options, those could be used for bunions, there are: Nonsteroidal anti-inflammatory drugs as: Acetaminophen, Etoricoxib and Tramadol, accommodative shoe with wide toe box and low heel, shoe stretching, bunion splints/braces, orthotics – medial arch support, metatarsal dome, toe spacers.

Operative-Surgical Treatment

There are >100 operations described for treating bunions [16]. The type of procedure performed is dependent on the severity of deformity, as well as the surgeon's preferences. Most patients will undergo some form of corrective

osteotomy, with or without an additional soft tissue procedure. The chevron and scarf osteotomies are both commonly used in Australia. Mild-to-moderate deformities are generally treated with a distal metatarsal osteotomy, and more severe deformities may require a proximal osteotomy or tarsometatarsal joint fusion. If there is severe arthritis (hallux rigidus), an MTPJ fusion may be indicated. Simple resection of the bony prominence (bunionectomy) is rare, as there is a high recurrence rate and patients are usually dissatisfied with the outcome [16]. Soft tissue procedures are also rarely performed in isolation and are more commonly used as an adjunct to osteotomy [16]. Minimally invasive surgery techniques are increasingly being used; however, the majority of studies show no difference in patient function, complication rates and clinical outcomes when compared with standard techniques [17]. Referral to an orthopaedic specialist is recommended if the patient has a painful prominence, has exhausted non-operative management and is a suitable operative candidate. The degree of functional impairment experienced and co-existing medical conditions are other considerations when deciding to refer. Patients with rheumatoid arthritis and diabetes may have additional foot concerns that require treatment. An examination of the lower limb and foot should be performed, as well as a simple gait assessment. Careful attention is required for overlying skin in patients with risk factors for breakdown and wound complications such as peripheral vascular disease and diabetes. If there is impending skin breakdown or ulceration, a more urgent referral is recommended. Juvenile bunion is one scenario in which delaying surgical intervention may be appropriate, as this should be avoided where possible until the patient reaches skeletal maturity [3]. Delaying surgery decreases the risk of recurrence and avoids damage to open growth plates [3], but this needs to be considered against the progression of deformity and possible later requirement of a more extensive correction. Referral can still be made; however, early surgery may not be offered. Weight-bearing anteroposterior, oblique and lateral foot radiographs should be performed. Arterial dopplers and diabetic screening can also be considered prior to referral. It is important to note that cosmesis alone is not an indication for operative management. Relief of pain is the main goal of surgery. While improved appearance and ability to wear desired footwear are secondary goals, a significant percentage of patients will still have difficulties with footwear following surgery, and some will still have cosmetic concerns [9,18]. Smoking is also a relative contraindication to surgery and is associated with increased wound complications, delayed union following osteotomy and poorer patient-reported outcomes [19–21]. Smoking cessation should be strongly encouraged. Following surgery, weight-bearing is allowed in a stiff-soled post-operative shoe, which is required for six weeks. Driving is not permitted until the patient has been cleared to return to normal footwear.

Non-Conventional Manual Techniques for a Treatment of Hallux Valgus

Alongside the traditional and conventional techniques of using posture correctors and/or surgery, there is an increasing tendency to resort to the use of physiotherapy procedures for the treatment of bunions, at the moment, after performing an operation [22-26]. Among these techniques, considered a miscellaneous of Physiotherapy and Osteopathy, there are: Bowen Technique, Reflexology and Su Jok. Bowen Technique [27–37] in one is non-invasive, manual technique, invented from Tom Bowen, applied on special acupuncture points in whole body, to increase self-healing. Reflexology [38,39] is an ancient method, based on specific points on the feet, for the activation of the end of nerves. Su Jok [40,41] is a Korean method also based on specific point on hands and feet,

more precise than Reflexology and with possibility to combine many different systems or points on the feet and fingers.

Molecular Docking for anti-inflammatory drugs, applied for plant deformities

The approach applied in this work, making use of the data obtained and reprocessed, deriving from the application of two different Molecular Docking software, has allowed us to highlight how natural, plant-based products, which we commonly find, could represent a future for the treatment of one of the most common diseases, currently, at the human level. The screening was carried out on the main molecules, used in a conventional pharmacological treatment for pain and inflammation in Hallux Valgus, as: Acetaminophen, Etoricoxib and Tramadol, and also on the chemical components present in a formulation of cream, applied before and during manual treatment, as Glycerin [42], as a base, with active substances as: Camphor [43] and Povidone Iodine [44]. We have used molecular docking software as 1-Click Docking [45]. The data that has been most taken into consideration is the binding affinity between the ligand and the target molecules as inflammatory mediators as: COX-1, COX-2, μ–Opioid Receptor, Post-synaptic Serotonine (5-HT) Receptor, Muscarinic Acetylcholine Receptor, Nicotinic Acetylcholine Receptor, MDMA Receptors and TRPA-1 Receptor. The bond affinity is returned with a value expressed in Kcal/mol, which can also be defined, if examined from a thermodynamic point of view, as the spontaneity of a reaction, linked to the concept of Gibbs Free Energy (ΔG), given by the relationship, expressed in Thermodynamics, $\Delta G=\Delta H-T\Delta S$, where H represents the Enthalpy value, an intrinsic characteristic of a thermodynamic system and, the S value represents the Entropy that is the degree of disorder of a thermodynamic system. If the reaction is spontaneous or exergonic, that is, it occurs with the release of energy in the external environment, then the final ΔG value will be negative. The more the ΔG value is negative, the more spontaneous the reaction is, as well as the bond between the ligand and its target molecule. Therefore, the more negative the ΔG value, expressed in Kcal/mol, the greater the bond affinity [46–49]. Therefore, to summarize, the more negative the numerical coefficient of Molecular Affinity, the greater the affinity itself between ligand and receptor and, therefore, the greater the pharmacological efficacy and the efficacy time of the ligand itself. Obviously, the time of efficacy/pharmacological action depends on the binding time between the ligand and the receptor. The more negative the molecular affinity value, the higher the affinity and the longer the interaction time will be. The analysis conducted, comparing the binding affinity values between conventional drugs and inflammatory mediators and the cream formulation, containing Glycerin, Camphor and Povidone Iodine, gave a greater binding affinity for the Camphor-based preparation and Povidone Iodine, proving that, once tested on subjects, they experienced a decrease in pain just after three applications, performed over two days (data not shown).

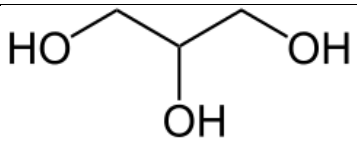
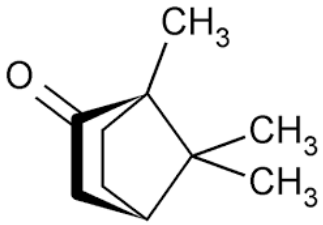
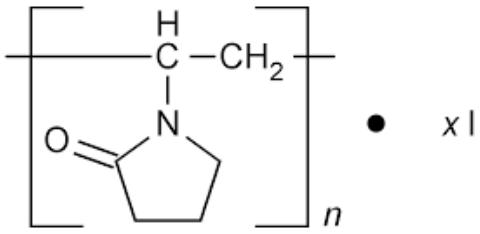
Materials and methods

Molecular Docking

The first part of the research consisted of a study, performed using the Molecular Docking method, on the main components of the preparation for topical administration, namely: Glycerin, Camphor and Povidone Iodine, Table 1. As mentioned initially, in the dedicated paragraph, at the level of the Introduction, all three components possess

proven anti-inflammatory properties and, the combination of the same, in a specific proportion, derives from the studies carried out by Thomas Bowen [data not shown] himself, the founder of the technique is reported here. Below is the composition, in percentage, of the aforementioned cream.

Table 1. Representation of composition, in percentage, of a cream, applied on bunions, before performing integrate treatment

Name	Structural Formula	Percentage of composition, on a total
Glycerin		75 %
Camphor		20 %
Povidone Iodine		5 %

In order to carry out the study, using the Molecular Docking 1-Click Docking software (https://mcule.com/apps/1-click-docking/) we used a computer, laptop, Toshiba Satellite L655-S5158 39.6 cm (15.6") HD Intel® Core ™ i3 4 GB DDR3-SDRAM 640 GB HDD, with Windows 10 Ultimate operating system. From an operational point of view, the aim was to determine the binding affinity between the main anti-inflammatory drugs used in analgesic therapy for Hallux Valgus, namely, Acetaminophen, Etoricoxib and Tramadol and their targets at the molecular level such as: COX-1, COX-1, mu Opioid Receptor, Serotonin Receptor, Muscarinic Receptor, Nicotinic Receptor, MDMA Receptor, TRPA-1 Receptor, and compare the values of this affinity, expressed in the form of the chemical bond energy value, having as the unit of measurement the KCal/mol, with the bond affinity found for the three main ones components present at the level of the preparation for topical administration, namely: Glycerin, Camphor and Povidone Iodine.

Applied Study

The applied study in question was carried out on a group of 30 subjects, divided on the basis of 5 criteria (Table 4), including 6 subjects within each classification category. The 5 categories, or criteria, of subdivision were:

(1) Six Female subjects, over 40 years old, with unilateral / unilateral deformation (at the level of a single foot);

(2) Six Female subjects, over 40 years old, with bilateral deformation (at the level of both feet);

(3) Six Male subjects, over 40 years of age, with bilateral deformation (at the level of both feet);

(4) Six Female subjects, less than 20 years old, with unilateral / unilateral deformation (at the level of a single foot);

(5) Six Male subjects, less than 20 years old, with unilateral / unilateral deformation (at the level of a single foot).

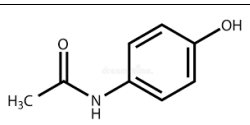
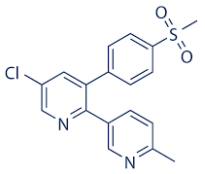
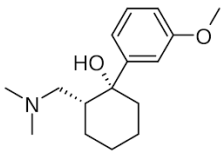
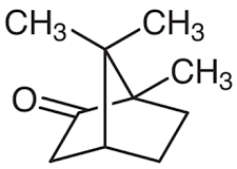
At the level of the five categories of subjects, a protocol of 10 treatments was applied, with a frequency of one treatment per week. The treatment consisted of two phases: the application of the preparation, topically administered, at the level of the plantar protusion, located at the level of the joint between the metatarsal and the proximal phalanx of the big toe and, subsequently, the integrated treatment was applied consisting of: Technique Bowen's, Reflexology and Su Jok, in synergistic combination. The duration of treatment for each individual subject was approximately one hour. Before and after the manual treatment, a morphological-anthropometric analysis was applied at the level of each individual subject, subdivided into the aforementioned categories, by processing photographic images, taken at the level of the same plantar deformation of the subjects, for the purpose to be able to notice if there had been a reduction in size (measured at the level of the major axis or longitudinal axis of the foot and at the level of the minor axis or latitudinal axis of the foot) of the protusion, present at the level of the joint between the metatarsus and the big toe. The reprocessing of the photographic images was carried out using an image software such as People Size 2020 [49] (https://openerg.com/psz/) and, for the statistical reprocessing of the data, deriving from the anthropometric reprocessing, the Graph Pad Prism statistical analysis software v.9.3.1 [50] (https://www.graphpad.com/). In order to be able to demonstrate the further effectiveness of the treatment, through the absence of long-term recurrence, each of the 30 subjects was called, at the end of the tenth and last session of manual manipulation, always at a frequency of once a week, for a period of 36 months (three years). In these sessions, the subject was examined from the point of view of the plantar deformation area and its measurements were taken for the subsequent anthropological-anthropometric analysis.

Results

The results obtained through the simulation model, i.e. through the Molecular Docking procedure, have highlighted how the preparation for topical administration, on the basis of the affinity data obtained, has a greater efficacy than conventional drugs that are applied as analgesics. Pain caused by plantar deformation. In particular, at the level of the last row at the bottom of Table 2 and Table 3, a virtual compound is shown created by the hypothetical reaction between: Glycerol/Glycerin, Camphor and Iodine Povidone (Table 1, Table 2, Table 3). It is not possible to rationalize and reduce to a single value since we have a single ligand with different targets, therefore, it is possible to examine each value, individually, and finally observe the totality of the obtained values. The virtual compound, which appears at the level of the last line, has a binding affinity value even almost double, for the COX-1 and COX-2 enzymes, i.e. -5.1 KCal/mol and -5.2 KCal/mol, against values such as: -2.4 KCal/mol and -2.7 KCal/mol for what concerns Acetaminophen, and -3.5 KCal/mol and -3.4 KCal/mol for what concerns Etoricoxib. This means that the binding affinity of the virtual compound, achieved by combining Glycerin, Camphor and Povidone Iodine, is greater for targets such as COX-1 and COX-2 than for conventional drugs such as Acetaminophen and

Etoricoxib. These and the subsequent affinity values, with the other reported receptors, express the efficacy of all three compounds, present at the level of the cream, in binding the main inflammatory mediators. Through an examination of the three-dimensional structure of the molecular target of the Tramadol and Camphor molecules, such as μ–Opioid Receptor, obtained through a 3D reconstruction, obtained from 1-Click Docking software, it was determined that both molecules, despite their completely different structure and origin, bind the same receptor portion, despite the fact that the amino acid residues involved in the bond are different; Gly 121 for Tramadol and Arg 48 for Camphor (Figure 1 and Figure 2).

Table 2. Values of bond affinity, determined through Molecular Docking, reported for conventional and unconventional drugs used in a treatment of Hallux Valgus, with amino acidic residues involved in bond between ligand and receptor

Ligand	Structure Formula	Receptor	Bond Affinity (Kcal/mol)	Amino acids Residues involved in bond
Acetaminophen		COX-1 COX-2	-2.4 -2.7	His 242 Leu 111
Etoricoxib		COX-1 COX-2	-3.5 -3.4	Asp 64 Glu 187
Tramadol		μ–Opioid Receptor Serotonin Receptor Muscarinic Receptor Nicotinic Receptor MDMA Receptor TRPA-1 Receptor	-4.7 0.0 -0.1 -5.4 0.0 0.0	Gly 121 / Pro 201 Asn 23 / /
Camphor		COX-1 COX-2 μ–Opioid Receptor Serotonin Receptor Muscarinic Receptor Nicotinic Receptor MDMA Receptor TRPA-1 Receptor	-4.4 -4.8 -3.3 0.0 -0.1 -4,1 0.0 0.0	Arg 48 Pro 21 Leu 56 / Phe 142 Pro 41 / /

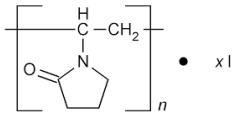
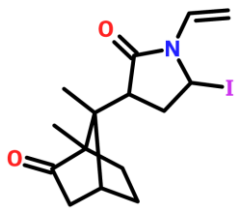
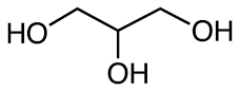
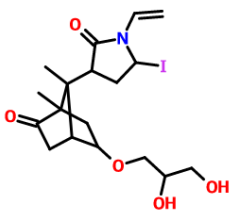
Povidon Iodine		COX-1 COX-2 μ–Opioid Receptor Serotonin Receptor Muscarinic Receptor Nicotinic Receptor MDMA Receptor TRPA-1 Receptor	-3.8 -3.7 -3.1 0.0 0.0 -3.1 0.0 0.0	His 221 Leu 57 Asp 59 / / Val 88 / /
Camphor + Povidone Iodine		COX-1 COX-2 μ–Opioid Receptor Serotonin Receptor Muscarinic Receptor Nicotinic Receptor MDMA Receptor TRPA-1 Receptor	-3.9 -4.0 -4.5 0.0 -0.1 -5.7 0.0 0.0	Met 44 Ile 176 Pro 12 / Asn 50 Leu 76 / /
Glycerol		COX-1 COX-2 μ–Opioid Receptor Serotonin Receptor Muscarinic Receptor Nicotinic Receptor MDMA Receptor TRPA-1 Receptor	-2.4 -2.6 -2.3 0.0 0.0 -2.9 0.0 0.0	Phe 222 Asp 98 Asn 131 / / Phe 85 / /
Glycerol + Camphor + Povidone Iodine		COX-1 COX-2 μ–Opioid Receptor Serotonin Receptor Muscarinic Receptor Nicotinic Receptor MDMA Receptor TRPA-1 Receptor	-5.1 -5.2 -4.8 0.0 0.0 -4.9 -1.1 0.0	His 111 Pro 94 Gln 75 / / Gly 233 Val 271 /

Table 3. Summary of the Molecular Affinity/Bond Affinity values of each type of remedy used to reduce the chronic inflammatory state at the level of plantar deformation

Ligand	**Receptor**	**Summation of the Molecular Affinity value (Kcal/mol)**
Acetaminophen	COX-1 COX-2	-5.1
Etoricoxib	COX-1 COX-2	-6.9
Tramadol	μ–Opioid Receptor Serotonin Receptor Muscarinic Receptor Nicotinic Receptor MDMA Receptor TRPA-1 Receptor	-10.2
Camphor	COX-1 COX-2 μ–Opioid Receptor Serotonin Receptor Muscarinic Receptor Nicotinic Receptor MDMA Receptor TRPA-1 Receptor	-16.7
Povidon Iodine	COX-1 COX-2 μ–Opioid Receptor Serotonin Receptor Muscarinic Receptor Nicotinic Receptor MDMA Receptor TRPA-1 Receptor	-13.7

Camphor + Povidone Iodine	COX-1 COX-2 μ–Opioid Receptor Serotonin Receptor Muscarinic Receptor Nicotinic Receptor MDMA Receptor TRPA-1 Receptor	-18.2
Glycerol	COX-1 COX-2 μ–Opioid Receptor Serotonin Receptor Muscarinic Receptor Nicotinic Receptor MDMA Receptor TRPA-1 Receptor	-10.2
Glycerol + Camphor + Povidone Iodine	COX-1 COX-2 μ–Opioid Receptor Serotonin Receptor Muscarinic Receptor Nicotinic Receptor MDMA Receptor TRPA-1 Receptor	-21.1

Table 4. Subdivision of the five groups of test subjects, with identification of: age, type of plantar deformation, localization of the same deformation and number of subjects for each group

Group	**Sex**	**Age (years)**	**Condition of the plantar deformation**	**Localization (if unilateral)**	**Number of participants per group**
1	F	≥ 40	Unilateral	Left Foot	6
2	F	≥ 40	Bilateral	/	6
3	M	≥ 40	Bilateral	/	6

4	F	≤ 20	Unilateral	Left Foot	6
5	M	≤ 20	Unilateral	Left Foot	6

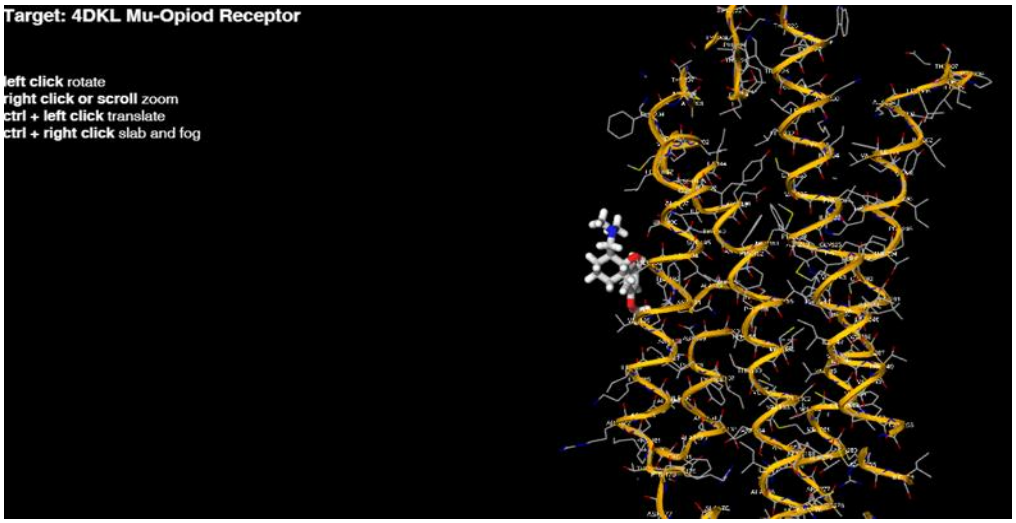


Figure 1. Molecule of Tramadol bound with μ–Opioid Receptor, obtained through tridimensional elaboration of 1-Click Docking Software

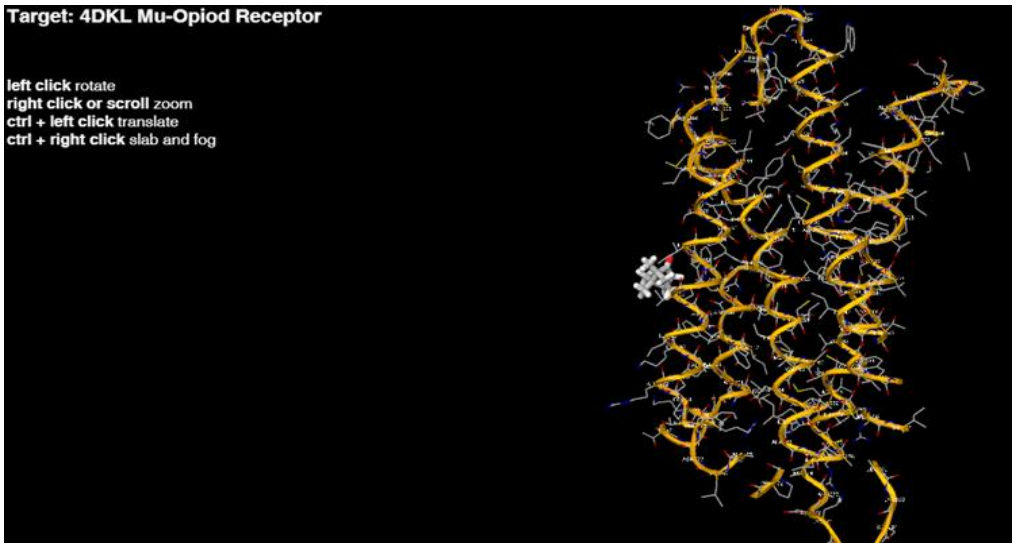


Figure 2. Molecule of Camphor bound with μ–Opioid Receptor, obtained through tridimensional elaboration of 1-Click Docking Software

To have a better understanding of the efficacy of preparations based on natural compounds, used as adjuvants in the treatment of plantar deformation, a summary of the Binding Affinity or Molecular Affinity data, determined by Molecular Docking was performed (Table 3). This measurement represents the most important datum since, within a good and robust level of approximation, the higher is the Molecular Affinity value (with a more negative numerical coefficient), the higher is the operating effectiveness of the same. In the case of products conventionally used for forms of chronic inflammation, such as: Acetaminophen, Etoricoxib and Tramadol, there is a Binding Affinity value, for each molecule, of: Acetaminophen: -5.1 Kcal/mol, Etoricoxib: -6.9 Kcal/ mol and Tramadol:

-10.2 Kcal/mol. The virtual compound, created by the molecular design of three molecules linked together, such as: Camphor, Iodine Povidone and Glycerol, gave a Binding Affinity value of -21.1 Kcal/mol. This value is very different from that found for the three conventional drugs, therefore, on the basis of what was stated above, a more negative value of the numerical coefficient of Molecular Affinity corresponds to a greater affinity between ligand and receptor and, therefore, a virtually major pharmacological efficacy. For this reason, the application of these natural products rather than conventional drugs was chosen.

Synergic combination of these three manual techniques such as: Bowen Technique, Reflexology and Su Jok, reveal success in: relief pain, reduce volume of bunions, reduce of inflammation, re alignment of feet and changing shape of the same, improve and regulate posture of whole body. For a good description and simplification of results we have decided to insert the values of the subjects of each group within a single graph, performing an arithmetic average between the values of the patients themselves. Among the patients belonging to the same group (intraspecific analysis), there are no factors that can profoundly influence a datum to the point of requiring the application of a weighted average, therefore, the application of an arithmetic average is admissible. Therefore, since there are 5 groups, each with 6 subjects, we have finally obtained 6 chart models. For subjects with bilateral plantar deformation, four graphs were obtained, two for each foot.

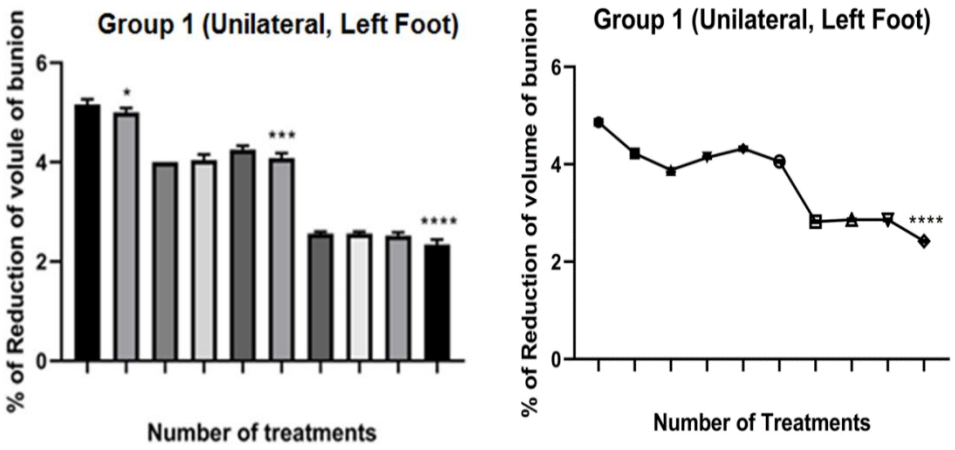
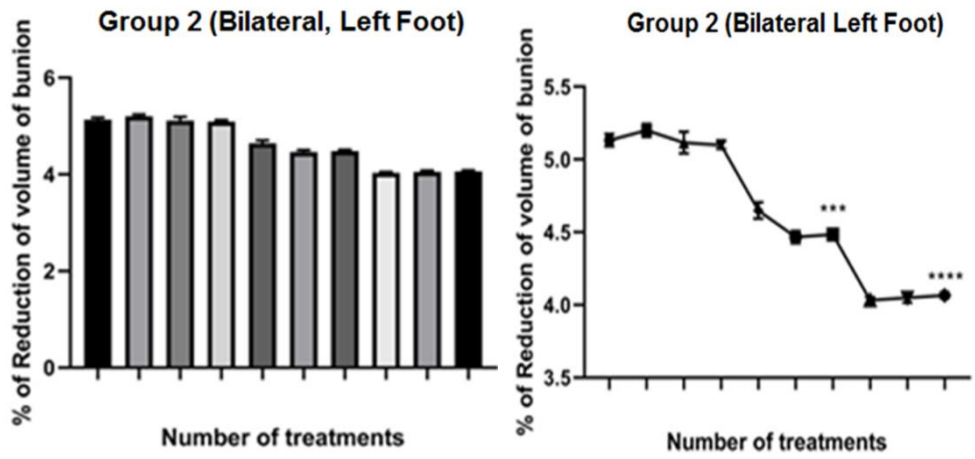


Figure 3. First Group of female subjects



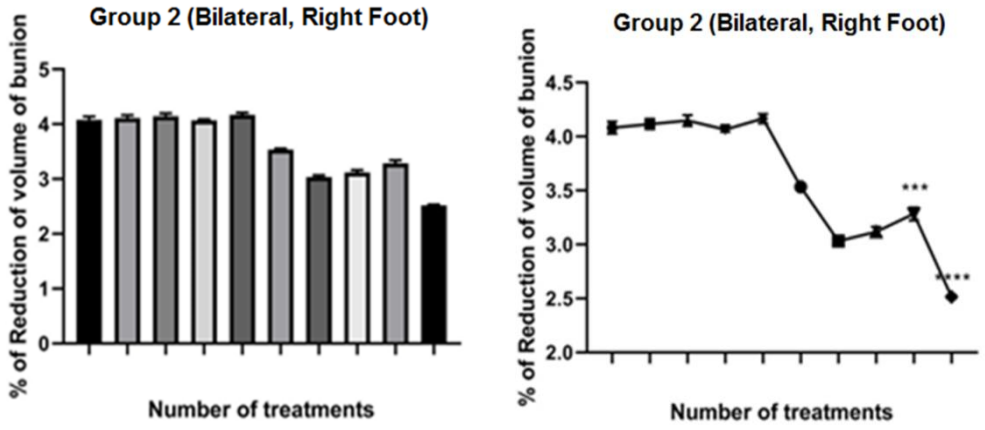
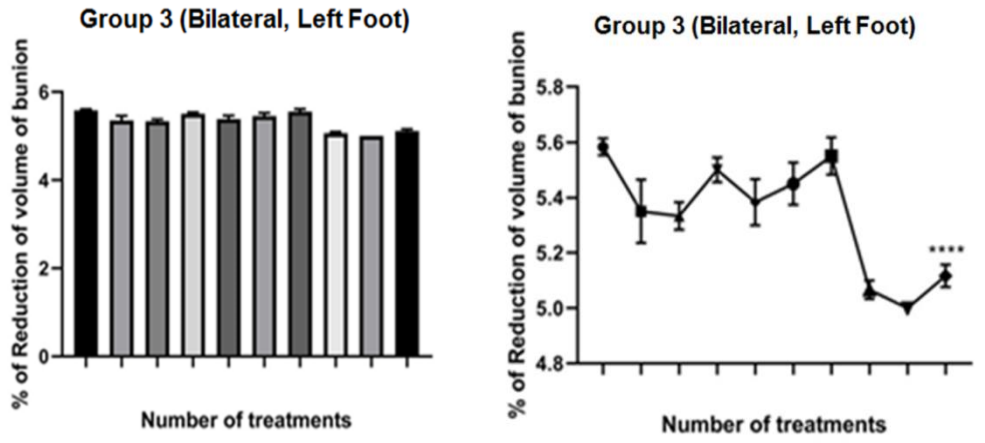


Figure 4. Second Group of female subjects

First case (Figure 3) of a group of six subjects, women, over 40 years, with unilateral hallux valgus deformity at the level of the right foot. At the beginning the deformity measured 5 mm in length (at the level of the major axis). After the application of 10 treatments of the three combined techniques, there was a reduction to 2 mm in length (at the level of the major axis). The graph shows the progressive reduction of the deformity size, up to the tenth treatment. Deformity reduction demonstrated a statistically significant correlation with high significance, with $\rho < 0.0001$.

The second case (Figure 4) refers to a group of six female subjects, over 40 years old, with bilateral deformation As in the first case, a protocol of ten integrated treatments was used (Bowen, Reflexology, Su Jok). The reason why two graphs are represented for each foot is in the measurement scale present on the axis of the ordinates of the graphs themselves. In the histogram chart there is no clear variation between the first and tenth treatment (last in the series), although there is a minimum SEM on each individual histogram. The reason lies in the fact that, the measurement scale shows values that are distant from each other by two units and, the variation of the dimension (measured at the level of the major axis) of the deformation, is of just one unit. In the secondary graphic model, that is represented with geometric figures and SEM in positive and negative, it is possible to appreciate the variation of the size of the deformity (at the level of both feet), moreover, thanks to the line of joining of the various points, it is possible appreciate the dynamics/kinetics of variation of the deformity size. Once again there is a statistically significant variation between the first and the last treatment, with $\rho < 0.0001$.



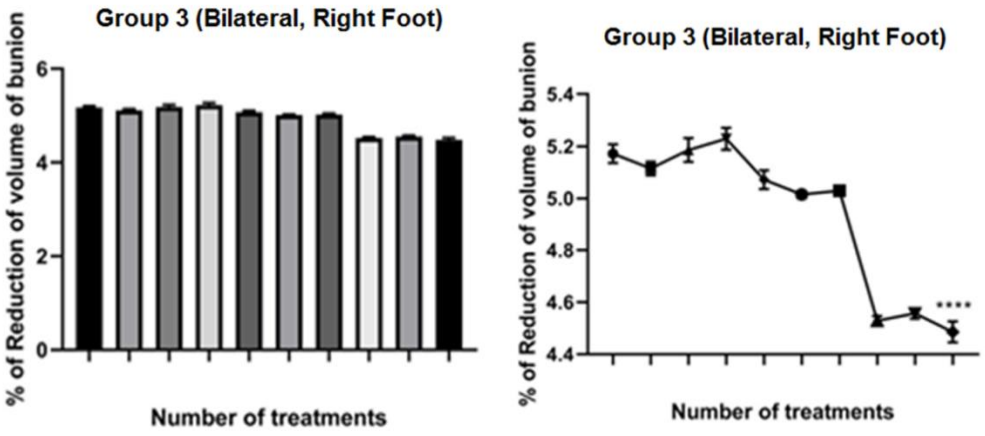


Figure 5. Third Group of male subjects

The third case (Figure 5) is refers to a group of six male subjects, over 40 years of age, with bilateral deformation As for the second case, the same protocol was used for ten integrated treatments and, also in this case, two graphs were represented in order to make the variation in the size of the deformity between the first and tenth treatment more comprehensible. In the dot representation, thanks once again, to the line of conjugation of the various points, it is possible to appreciate the dynamics / kinetics of variation of the size of the deformity. In this case, it is possible to notice how, in the right foot, only after 8 treatments, it is possible to appreciate a statistically significant reduction in the deformity. Once again there is a statistically significant variation, with high significance, between the first is the last treatment, with $\rho < 0.0001$.

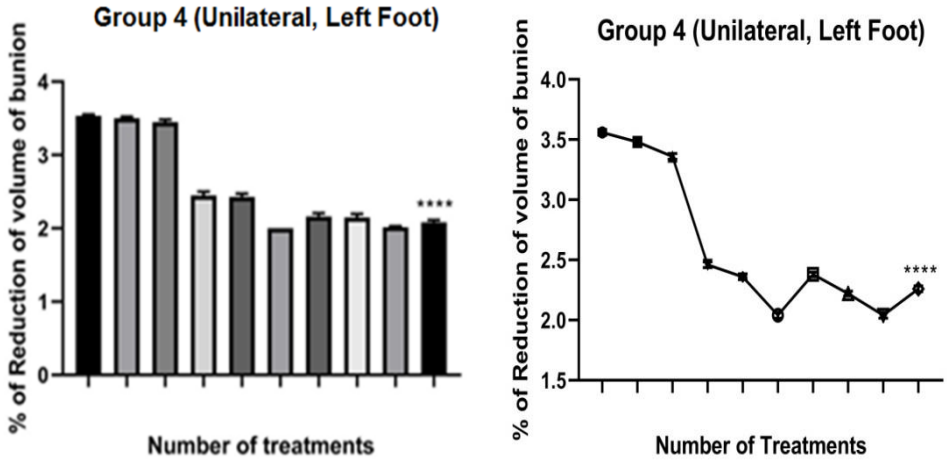


Figure 6. Fourth Group of female subjects

The fourth case (Figure 6) refers to a group of six female subjects, less than 20 years old, with unilateral deformation. For better exposure and interpretation of the results, it was also chosen in this case to perform a two-graph representation, whose dynamics / kinetics of size reduction, allows us to extrapolate how the integrated treatment, had an effect after a series of seven treatments. As for the previous measurements it is possible to notice how there is a statistically significant variation, with high significance, between the first and the last treatment ($\rho < 0.0001$).

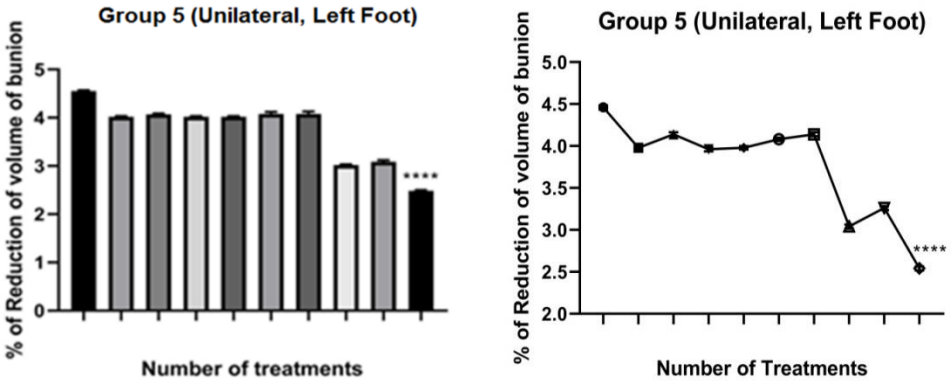


Figure 7. Fifth Group of male subjects

The fifth and last case (Figure 7) refers to a group of six male subjects, less than 20 years old, with unilateral deformation. Given the visible variation directly through the histogram graph, it was not necessary to resort to the points graph. for both feet it was possible to notice the statistically significant variation, with high significance, between the first and the tenth and last treatment ($\rho < 0.0001$).

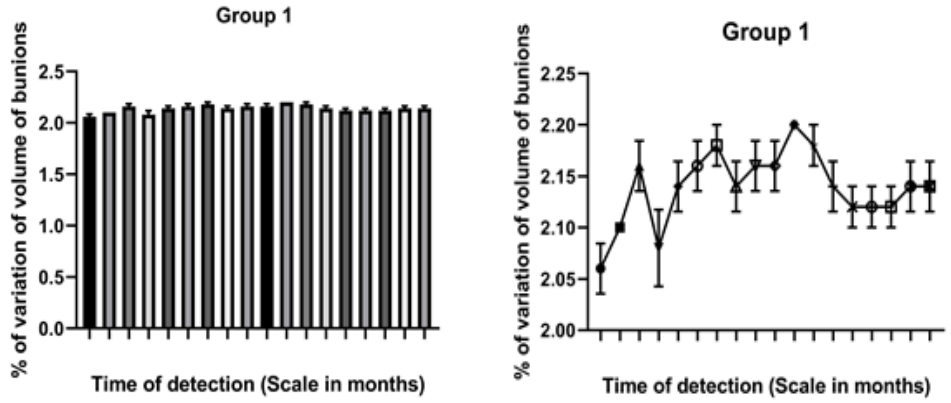


Figure 8. Graphic reworking on Group 1 of subjects, during the period of three years, after sessions of treatment, for the evaluation of any volume variation in the area of plantar deformation

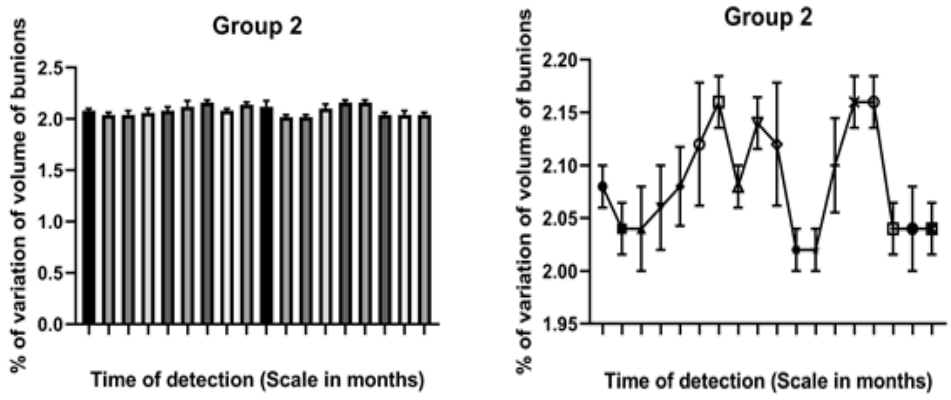


Figure 9. Graphic reworking on Group 2 of subjects, during the period of three years, after sessions of treatment, for the evaluation of any volume variation in the area of plantar deformation

Group 1 of female subjects, having a unilateral deformation in the left foot, at the end of the ten treatment sessions and 36 months of control measurements, did not show a significant change, calculating from the beginning of the control period, until at the end of the same (Figure 8). As can be seen in the graph of the same Figure 8, at the end of the treatment, the deformation had a diameter of just over 2.05 cm. At the end of 36 months, the diameter was about 2.15 cm.

Group 2 of female subjects, having a bilateral deformation at the level of both plantar extremities, did not have any type of significant change in the diameter of the plantar deformation. Indeed, calculating the variation, from the initial exam to the final one, from a global point of view, there was a decrease at the end of the 36 months (Figure 9). From an initial diameter, after treatment, of about 2.08 cm, after three years of control, we arrived at a value of less than 2.05 cm.

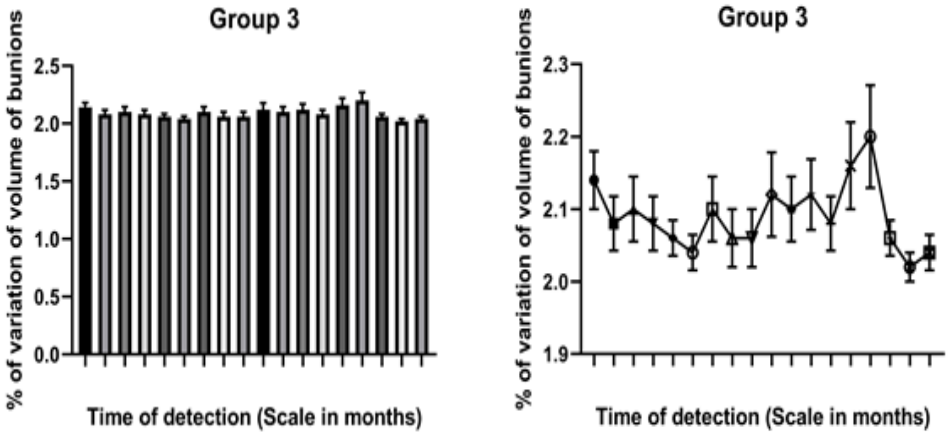


Figure 10. Graphic reworking on Group 2 of subjects, during the period of three years, after sessions of treatment, for the evaluation of any volume variation in the area of plantar deformation

Group 3 of male subjects, having, at the beginning of the treatment, a bilateral deformation, at both plantar extremities, at the end of the 36-month follow-up, showed a reduction in the diameter of the deformation zone (Figure 10). It starts from a value of about 2.15 cm in diameter, to reach 2.05 cm at the end of the control period.

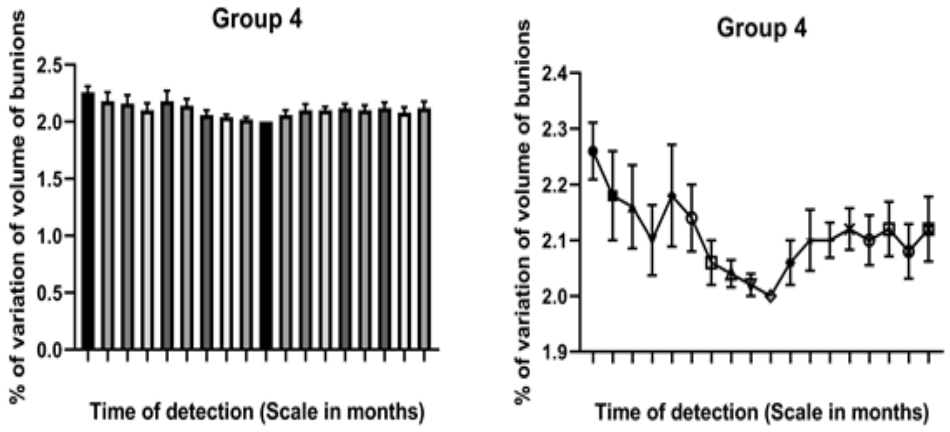


Figure 11. Graphic reworking on Group 4 of subjects, during the period of three years, after sessions of treatment, for the evaluation of any volume variation in the area of plantar deformation

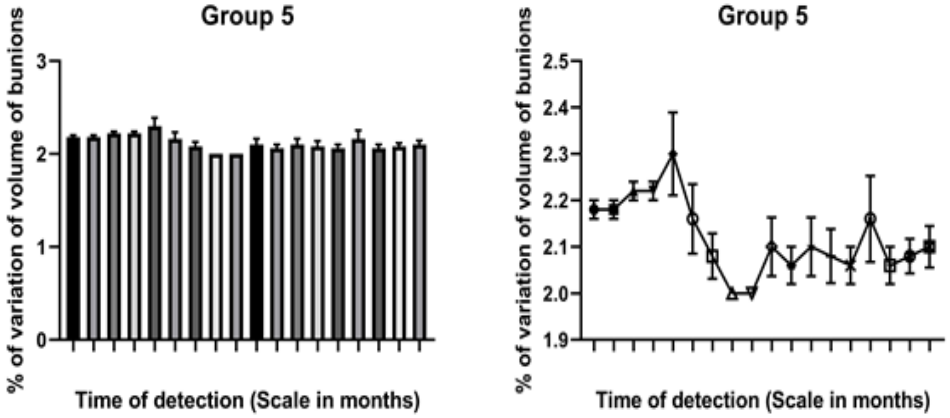


Figure 12. Graphic reworking on Group 5 of subjects, during the period of three years, after sessions of treatment, for the evaluation of any volume variation in the area of plantar deformation

Similarly to Group 3, also Group 4 of female subjects, aged less than or equal to 20 years, and unilateral deformation at the level of the left foot (Figure 11), showed a slight reduction in the diameter of the area of plantar deformation, at the end of the 36 months of follow-up. From an initial diameter of about 2.25 cm, we arrive at about 2.1 cm.

Group 5 of male subjects, aged less than or equal to 20 years and with unilateral deformation at the level of the left foot (Figure 12), also showed a reduction in the diameter of the zone, corresponding to the plantar deformation, from the initial state to the final one. From a value of about 2.19 cm there was a decrease to about 2.1 cm.

These graphs have not been represented with the value of statistical significance since, only in the presence of a statistically significant result ($\rho < 0.05$) of increase in the volume of the plantar deformation area, would it have been reported.

Discussion

The analysis performed using Molecular Docking essentially aimed to compare conventional molecules, used in pain therapy for plantar deformities, with a new product, topically administered, made from the mixed combination of three naturally derived compounds. They showed a greater binding affinity for the main receptors involved in the inflammatory process than conventional drugs. At the level of the applied research, which has been conducted on subjects, the topical application of the cream, during each procedure of integrated manual treatment (deriving from the synergistic fusion of techniques such as: Bowen Technique, Reflexology and Su Jok), was a powerful adjuvant of the therapy and was also recommended to patients for a form of personalized treatment, to be performed at home. The anthropometric study performed on the diameter of the plantar deformation, before and after manual treatment, showed a reduction, with a very high level of statistics significance ($\rho < 0{,}0001$ - ****), in all groups of patients treated, without any difference between the factors taken into consideration such as: age and sex and unilateral or bilateral deformation. Furthermore, the subsequent 36-month follow-up period served as a time-dependence experiment to demonstrate no increase in plantar deformation volume. Indeed, in some cases, such as Groups 2, 3, 4, 5, there was a decrease in the diameter of the area, corresponding to the plantar deformation. This is proof of the

high operational effectiveness of the technique disclosed here. The final result is a synergistic summation between the data obtained through the Molecular Docking procedure, which showed how natural compounds, used as an adjunct to integrated manual manipulation treatment, had a greater affinity for the targets (molecules involved in inflammation processes) than the drugs used in canonical therapy, and the combined action of the three manual manipulation techniques, that have shown both the ability to significantly reduce plantar deformation and, more importantly, to avoid its long-term recrudescence.

Conclusions

The studies reported here have allowed us to conclude the following: the applied study has highlighted how a combination of manual techniques, coupled with a topical treatment of natural compounds, can successfully resolve the plantar deformation known as Hallux Valgus, without resorting to surgery and without any form of recrudescence in all of groups of subjects. Furthermore, given the result obtained with Molecular Docking, in which the combination of natural compounds has a greater affinity than the drugs used in conventional pain therapy, it is possible to assume, with a high statistical probability, that the data of computerized modeling and those of the applied study, are associable. We reserve further experiments, on larger subjects cohorts, in order to confirm the results obtained in this first research.

Declarations

Source of Funding

The work reported here was conducted with the assistance of the company Worldwide Consultancy & Services (https://en.worldwideeurope.com/), with registered office located in Via Andrea Ferrara 45 - 00165, Rome, Italy. The company enjoys the following Certification Systems: UNI EN ISO 9001: 2015, ISO 21001: 2019, UNI EN 16775: 2016, UNI EN ISO 20700: 2018, UNI / TR 11594: 2015.

Conflicts of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethical Statement

This study was conducted with the prior approval of the ethics committee specifically set up by Worldwide Consultancy & Services, defined as the Worldwide Ethics Committee (https://en.worldwideeurope.com/general-8). The Numerical Code of Approval of the Ethics Committee is the following: WCS-WEC.1/2023.

Author Contributions

Aleksandra Maksimovic: Conceptualization, Methodology, Project administration, Supervision, Visualization. Stefano Turini: Data curation, Formal Analysis, Investigation, Software, Validation, Writing original draft.

Consent for publication

Authors declare that they consented for the publication of this research work.

Availability of data and materials

All data and materials are available in the main text.

Acknowledgements

The authors would like to thank in particular the Physiotherapy Assistant Ljubica Tesic, member of ALVITA PLUS D.O.O., for her contribution and help provided in carrying out the applied study.

References

[1] Menz HB, Harrison C, Britt H, Whittaker GA, Landorf KB, Munteanu SE. Management of hallux valgus in general practice in Australia. Arthritis Care Res (Hoboken) 2019. doi: 10.1002/acr.24075 [ePub ahead of print].

[2] Nix S, Smith M, Vicenzino B. Prevalence of hallux valgus in the general population: A systematic review and meta-analysis. J Foot Ankle Res 2010;3:21. doi: 10.1186/1757-1146-3-21.

[3] Chell J, Dhar S. Pediatric hallux valgus. Foot Ankle Clin 2014;19(2):235–43. doi: 10.1016/j.fcl.2014.02.007.

[4] Coughlin MJ, Jones CP. Hallux valgus: Demographics, etiology, and radiographic assessment. Foot Ankle Int 2007;28(7):759–77. doi: 10.3113/FAI.2007.0759.

[5] Coughlin MJ. Instructional course lectures, The American academy of orthopaedic surgeons – Hallux valgus. J Bone Joint Surg Am 1996;78(6):932–66.

[6] Menz HB, Morris ME, Lord SR. Foot and ankle risk factors for falls in older people: A prospective study. J Gerontol A Biol Sci Med Sci 2006;61(8):866–70. doi: 10.1093/gerona/61.8.866.

[7] Hannan MT, Menz HB, Jordan JM, Cupples LA, Cheng C-H, Hsu Y-H. Hallux valgus and lesser toe deformities are highly heritable in adult men and women: The Framingham foot study. Arthritis Care Res (Hoboken) 2013;65(9):1515–21. doi: 10.1002/acr.22040.

[8] Nix SE, Vicenzino BT, Collins NJ, Smith MD. Characteristics of foot structure and footwear associated with hallux valgus: A systematic review. Osteoarthritis Cartilage 2012;20(10):1059–74. doi: 10.1016/j.joca.2012. 06.007.

[9] Torkki M, Malmivaara A, Seitsalo S, Hoikka V, Laippala P, Paavolainen P. Surgery vs orthosis vs watchful waiting for hallux valgus: A randomized controlled trial. JAMA 2001;285(19):2474–80. doi: 10.1001/jama.285. 19.2474.

[10] Kilmartin TE, Barrington RL, Wallace WA. A controlled prospective trial of a foot Orthosis for juvenile hallux valgus. J Bone Joint Surg Br 1994 Mar;76(2):210–14. doi: 10.1302/0301- 620X.76B2.8113278.

[11] Nakagawa R, Yamaguchi S, Kimura S, et al. Efficacy of foot orthoses as nonoperative treatment for hallux valgus: A 2-year follow-up study. J Orthop Sci 2019;24(3):526–31. doi: 10.1016/j.jos.2018.11.003.

[12] Plaass C, Karch A, Koch A, et al. Short term results of dynamic splinting for hallux valgus –A prospective randomized study. Foot Ankle Surg 2020;26(2):146–50. doi: 10.1016/j.fas.2019.01.002.

[13] Tehraninasr A, Saeedi H, Forogh B, Bahramizadeh M, Keyhani MR. Effects of insole with toe-separator and night splint on patients with painful hallux valgus: A comparative study. Prosthet Orthot Int 2008;32(1):79–83. doi: 10.1080/03093640701669074.

[14] Vanore JV, Christensen JC, Kravitz SR, et al. Diagnosis and treatment of first metatarsophalangeal joint disorders. Section 1: Hallux valgus. J Foot Ankle Surg 2003;42(3):112–23. doi: 10.1016/s1067-2516(03)70014-3.

[15] Ferrari J, Higgins JP, Prior TD. Interventions for treating hallux valgus (abducto valgus) and bunions. Cochrane Database Syst Rev 2004;(1):CD000964. doi: 10.1002/14651858.CD000964.pub2.

[16] Easley ME, Trnka HJ. Current concepts review: Hallux valgus part II: Operative treatment. Foot Ankle Int 2007;28(6):748–58. doi: 10.3113/ FAI.2007.0748.

[17] Lu J, Zhao H, Liang X, Ma Q. Comparison of minimally invasive and traditionally open surgeries in correction of hallux valgus: A metaanalysis. J Foot Ankle Surg 2020;59(4):801–06. doi: 10.1053/j.jfas.2019.03.021.

[18] Mann RA, Rudicel S, Graves SC. Repair of hallux valgus with a distal soft-tissue procedure and proximal metatarsal osteotomy. A long-term follow-up. J Bone Joint Surg Am 1992;74(1):124–29.

[19] Krannitz KW, Fong HW, Fallat LM, Kish J. The effect of cigarette smoking on radiographic bone healing after elective foot surgery. J Foot Ankle Surg 2009;48(5):525–27. doi: 10.1053/j.jfas.2009.04.008.

[20] Beahrs TR, Reagan J, Bettin CC, Grear BJ, Murphy GA, Richardson DR. Smoking effects in foot and ankle surgery: An evidence-based review. Foot Ankle Int 2019;40(10):1226–32. doi: 10.1177/1071100719867942.

[21] Pearson RG, Clement RGE, Edwards KL, Scammell BE. Do smokers have greater risk of delayed and non-union after fracture, osteotomy and arthrodesis? A systematic review with meta-analysis. BMJ Open 2016;6(11):e010303. doi: 10.1136/bmjopen-2015-010303.

[22] B Zirngibl, J Grifka, C Baier, J Götz . [Hallux Valgus: Etiology, Diagnosis, and Therapeutic Principles] Orthopade 46 (3), 283-296 Mar 2017.

[23] No authors listed. Bunion: Strengthening Foot Muscles to Reduce Pain and Improve Mobility. J Orthop Sports Phys Ther, 46 (7), 606 Jul 2016. doi: 10.2519/jospt.2016.0504.

[24] Lukas Fraissler, Christian Konrads, Maik Hoberg, Maximilian Rudert, Matthias Walcher . Treatment of Hallux Valgus Deformity. EFORT Open Rev, 1 (8), 295-302 2016 Aug 25 eCollection Aug 2016.

[25] Ward M. Glasoe. Treatment of Progressive First Metatarsophalangeal Hallux Valgus Deformity: A Biomechanically Based Muscle-Strengthening Approach. J Orthop Sports Phys Ther, 46 (7), 596-605 Jul 2016.

[26] Suzanne T. Hawson. Physical Therapy Post-Hallux Abducto Valgus Correction. Clin Podiatr Med Surg, 31 (2), 309-22 Apr 2014.

[27] Baker, J., 2013. Bowen Unravelled: a Journey into the Fascial Understanding of the Bowen Technique. Lotus Publishing. Benjamin, M., 2009. The fascia of the limbs and back e a review. J. Anat. 214, 1e18. Black, L., Murray, C., 2005. ISBT - Bowen Therapy: Foundation Course. International School of Bowen Therapy.

[28] Carter, B., 2002a. Clients' experiences of frozen shoulder and its treatment with Bowen technique. Complement. Ther. Nurs. Midwifery 8, 204e210. Carter, B., 2002b. A pilot study to evaluate the effectiveness of Bowen technique in the management of clients with frozen shoulder. Complement. Ther. Med. 9, 208e215.

[29] Duncan, B., Mchugh, P., Houghton, F., Wilson, C., 2011. Improved motor function with Bowen therapy for rehabilitation in chronic stroke: a pilot study. J. Prim. Health Care 3.

[30] Fernandez-de-Las-Penas, C., Alonso-Blanco, C., Cleland, J.A., Rodriguez-Blanco, C., Alburquerque-Sendin, F., 2008. Changes in pressure pain thresholds over C5-C6 zygapophyseal joint after a cervicothoracic junction manipulation in healthy subjects. J. Manip. Physiol. Ther. 31, 332e337.

[31] Frank, L., Mclaughlin, P., Vaughan, B., 2013. The repeatability of pressure algometry in asymptomatic individuals over consecutive days. Int. J. Osteopath. Med. 16 (3), 143e152.

[32] Hansen, C., Taylor-Piliae, R.E., 2011. What is Bowenwork(R)? A systematic review. J. Altern. Complement. Med. 17, 1001e1006.

[33] Hansen, C.A., 2012. A Pilot Study on Bowen work® for Symptom Management of Women Breast Cancer Survivors with Lymphedema. The University of Arizona.

[34] Jones, D., 2004. The Effect of Osteopathic Manipulative Therapy Applied to the Lumbar Spina on Postural Stability: a Pilot Study. Victoria University.

[35] Marr, M., Baker, J., Lambon, N., Perry, J., 2011. The effects of the Bowen technique on hamstring flexibility over time: a randomised controlled trial. J. Bodyw. Mov.Ther. 15, 281e290.

[36] Whitaker, J., Gilliam, P., Seba, D., 1997. The Bowen technique - a gentle hands-on method that affects the autonomic nervous system as measured by heart rate variability and clinical assessment. In: 32nd Annual Conference of American Academy of Environmental Medicine (California).

[37] Yadav, S.K., 2013. Comparative Study between the Effectiveness of Bowen Technique and Dynamic Soft Tissue Mobilization in Increasing Hamstring Flexibility. Master thesis. Rajiv Gandhi University of Health Sciences.

[38] Soheila Moghimi-Hanjani, Zahra Mehdizadeh-Tourzani, Mahnaz Shoghi. The Effect of Foot Reflexology on Anxiety, Pain, and Outcomes of the Labor in Primigravida Women. Acta Med Iran, 53 (8), 507-11 Aug 2015.

[39] Hyun Jin Song, Sun Mi Choi, Hyun-Ju Seo, Heeyoung Lee, Heejeong Son, Sanghun Lee. Self-administered Foot Reflexology for the Management of Chronic Health Conditions: A Systematic Review. J Altern Complement Med, 21 (2), 69-76 Feb 2015.

[40] M I Safonov, M V Naprienko [Analysis of the Efficacy of Reflexology in the Complex Treatment of Chronic Migraine]. Zh Nevrol Psikhiatr Im S S Korsakova, 117 (5), 22-25 2017.

[41] A M Ubaĭdullaev, G Kh Sharafutdinova, Sh U Ismailov. [Treatment of Bronchial Asthma by the Su-Jok Therapy Method]. Ter Arkh, 70 (12), 44-6 1998.

[42] E Szél, H Polyánka, K Szabó, P Hartmann, D Degovics, B Balázs, I B Németh, C Korponyai, E Csányi, J Kaszaki, S Dikstein, K Nagy, L Kemény, G Erős. Anti-irritant and anti-inflammatory effects of glycerol and xylitol in sodium lauryl sulphate-induced acute irritation. J Eur Acad Dermatol Venereol. 2015 Dec;29(12):2333-41. doi: 10.1111/jdv.13225. Epub 2015 Sep 14. PMID: 26370610.

[43] Elisangela Dos Santos, Maicon Matos Leitão, Caren Naomi Aguero Ito, Saulo Euclides Silva-Filho, Arielle Cristina Arena, Francielli Maria de Souza Silva-Comar, Roberto Kenji Nakamura Cuman, Rodrigo Juliano Oliveira, Anelise Samara Nazari Formagio, Cândida Aparecida Leite Kassuya. Analgesic and anti-inflammatory articular effects of essential oil and camphor isolated from Ocimum kilimandscharicum Gürke leaves. J Ethnopharmacol. 2021 Apr 6;269:113697. doi: 10.1016/j.jep.2020.113697. Epub 2020 Dec 13. PMID: 33316364.

[44] K Senthil Kumar, G Vinay Kumar Reddy, Gayathri Naidu, Rajesh Pandiarajan. Role of povidone iodine in periapical surgeries: Hemostyptic and anti-inflammatory? Ann Maxillofac Surg. 2011 Jul;1(2):107-11. doi: 10.4103/2231-0746.92768. PMID: 23483078 PMCID: PMC3591019.

[45] https://mcule.com/apps/1-click-docking/.

[46] Garrett M Morris, Marguerita Lim-Wilby. Molecular docking. Methods Mol Biol. 2008;443:365-82. doi: 10.1007/978-1-59745-177-2_19.

[47] Veronica Salmaso and Stefano Moro. Bridging Molecular Docking to Molecular Dynamics in Exploring Ligand-Protein Recognition Process: An Overview. Front. Pharmacol., 2018. doi: 10.3389/fphar.2018.00923.

[48] Andreas Kukol. Molecular Modeling of Proteins. ISBN: 978-1-58829-864-5 e-ISBN: 978-1-59745-177-2, doi: 10.1007/978-1-59745-177-2, ISSN: 1064-3745, Library of Congress Control Number: 2007942569 ©2008 Humana Press, a part of Springer Science+Business Media, LLC.

[49] https://openerg.com/psz/

[50] https://www.graphpad.com/