Mini Review

Historical Course of Neuropsychiatric Effects of Lemon Balm (*Melissa officinalis* L.) as a Medicinal Herb

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Article Info

Abstract

Affective disorders have become prevalent and costly worldwide chronic conditions. Lemon Balm (*Melissa officinalis* L.) is a medicinal plant with beneficial effects on neuropsychiatric disorders. Its potential to specifically treat conditions such as depression and anxiety has been investigated for over 20 centuries. Given the lack of a historical overview of lemon balm in mood disorders, the present review aimed to introduce the historical course of the neuro-psychiatric applications of lemon balm across the centuries. We investigated several viable medieval Arabic sources up to the 15th century, to distinguish the neuropsychiatric applications, especially anxiolytic and anti-depressive effects of lemon balm. In the early centuries, lemon balm was mainly prescribed to treat gastrointestinal disorders. Over time, physicians identified the efficient use of lemon balm in sadness, sleep disorders, anxiety, depression, epilepsy, ischemic stroke, amnesia, sciatalgia, and radicular neuropathy. Importantly, it was established that the therapeutic effects of lemon balm in the field of neuro-psychiatric diseases were emphasized by physicians during the Middle Ages. These findings have since been validated in human clinical trials. Lemon balm has also demonstrated the ability to be utilized in epilepsy, amnesia and ischemic stroke. Based on the extensive history of lemon balm in neuropsychiatry, future investigations could use this knowledge to extensively investigate the potential of lemon balm in neuropsychiatric disorders such as depression and anxiety, and possibly develop an efficient neuropsychiatric remedy.

Introduction

The incidence of chronic diseases, which includes an array of psychiatric conditions are exponentially on the rise. Consequently, anxiety disorders have become the most prevalent psychiatric disorders, while depression is the fourth most common and economically expensive psychiatric disorder.[1,2] In recent decades, physicians have been interested in alternative and complementary therapies, particularly medicinal herbs in the field of mental health.[3-5] Alongside a body of literature that points to the therapeutic effects of medicinal herbs, studies indicate that herbs are generally well tolerated and easily accessible to patients.[6,7]

Treatments involving herbal interventions have an enduring history, dating back to as early as the existence of mankind.[8] Lemon balm (*Melissa officinalis* L.) is an herb that belongs to the lamiaceae family. The lamiaceae species of flowering plants comprise white-colored flowers, which release a lemony aroma. Lemon balm is a well-known and highly consumed medicinal herb in central and southern Europe, the Mediterranean region, and west Asia.[9] According to manuscripts originating from Greece that were conceptualized 2000 years ago, lemon balm was utilized as a medicinal plant and used as an exhilarator, anti-depressant, anxiolytic, hypnotic, and sedative.[10,11] In the last two decades, clinical trials have evaluated the effects of lemon balm on various central nervous system functions, continuing to demonstrate anxiolytic and anti-depressive properties, in addition to reducing insomnia, elevating neuroprotection, and enhancing cognitive and

memory function.[9,11,12]

With medieval translation movements beginning in the 7th and 8th centuries, the scientific literature relating to the lemon balm that followed these centuries was translated into Arabic,[13,14] the common language of the scientific literature in vast areas of Asia, Africa, and certain parts of Europe during this time.[15,16] By reviewing the Arabic literature till the 15th century, valuable historical information regarding the neuropsychiatric applications of lemon balm can be derived (Figure 1).[17] To the best of our knowledge, a comprehensive historical review has not been conducted to focus attention on the effects of lemon balm on affective disorders such as depression and anxiety. Therefore, in the present review, we examined the neuropsychiatric applications of lemon balm using a number of viable sources including medical books, pharmacopoeia and publications, available on well-known online databases. The aim of the present review was to provide a historical overview of the efficacy of lemon balm in mood disorders, particularly anxiety and depression.

Early Centuries

The book titled "De material Medica" (published by Dioscorides) is regarded as the first pharmaceutical
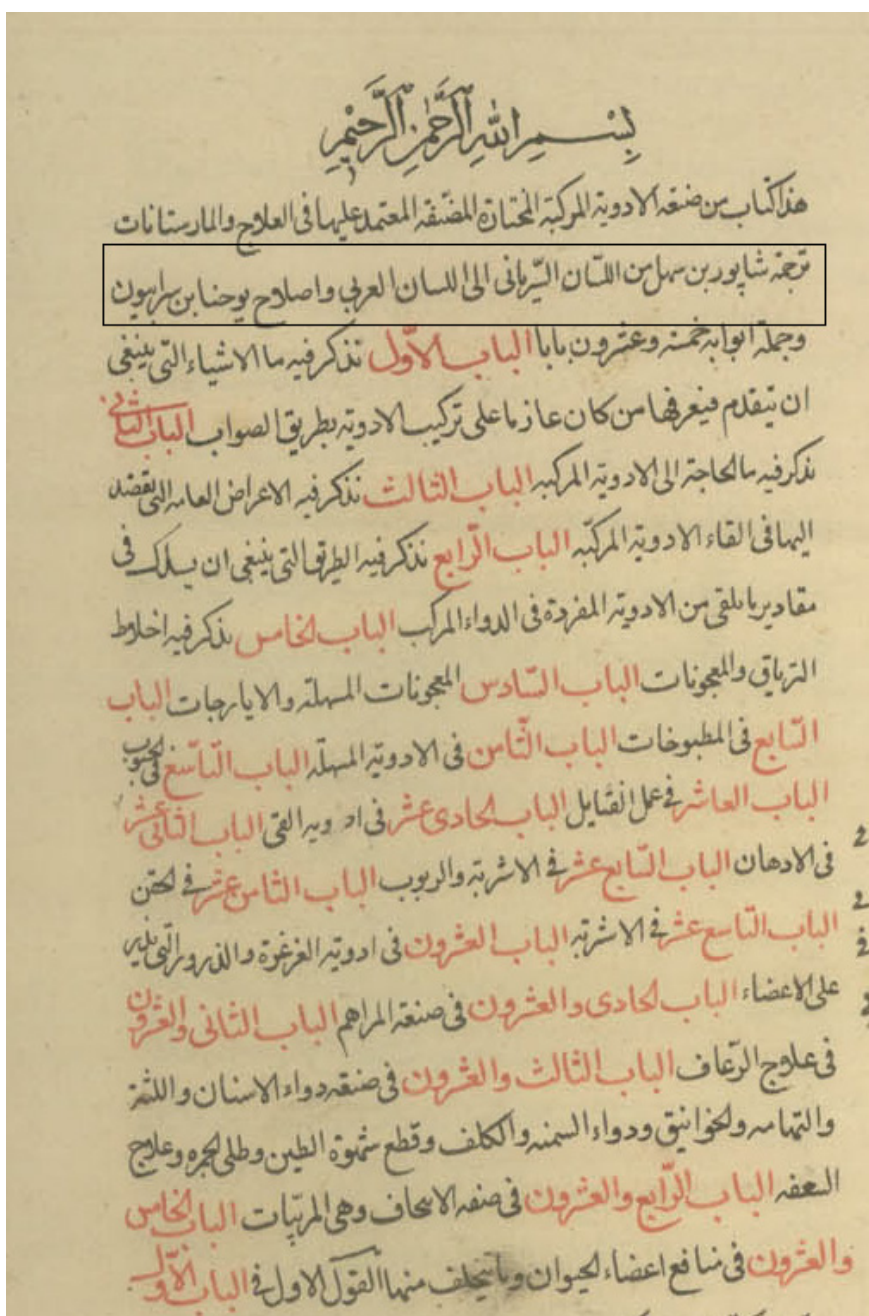

Figure 1. An example of the translation of medical books into Arabic during the translation movement. "Al-Adwiya al-Murakabba" (Aqrabadhin).[17] The content of the book relates to how to make compound drugs which has been translated from Syriac into Arabic by Shapur bin Sahl, a 9th century Jundishapur physician.

encyclopedia in the history of medicine.[18] However, lemon balm, which is referred to as "Milissophullon", was not applied to psychiatric or central nervous system health within this source. Instead, Galen (129-210 A.D) was the first to point out the efficacy of lemon balm in the treatment of psychiatric and nervous system disorders.[19]

9th Century

During the ninth century (800-900 AD), three main works called "al-Adwiya al-Murakabba" (Aqrabadhin) by Shapur ibn Sahl,[19] "Firdous al-Hikmah" (Paradise of Wisdom) by Ali ibn Sahl Rabban al-Tabari,[20,21] and "al-dhakhīrah fī 'ilm al-ṭibb" (Treasure in Medicine) by Thābit ibn Qurra,[22] were published. These sources highlighted the potential of lemon balm to alleviate anxiety-induced palpitations, fear, despondency, feelings of faintness, melancholia, sadness, obsessive disorder symptoms, panic as well as the ability to enhance positive mood states.

10th Century

Muhammad ibn Zakariya al-Razi (*Rhazes*), a prominent physician and clinician during the 10th century, emphasized the pharmacological effects of lemon balm, which included anti-depressive effects.[23] The importance of lemon balm in the treatment of psychiatric disorders, especially severe depression was also called to attention.[24] Additional findings (in a source known as "Abdal-al-Adwiya") further suggested the involvement of lemon balm as a mood enhancer and an intervention for improving depressive mood states.[25] *Rhazes*[23] also highlighted the capacity of lemon balm to treat neurological disorders such as epilepsy and amnesia.[26] Ali ibn al-Abbas al-Majusi (Latinized as *Haly Abbas)* was another well-known 10th century physician, who prescribed lemon balm as a memory enhancer, therapy for anxiety, amnesia, and headaches in neuropsychiatric disorders.[27]

11th Century

Husain Bin Abdullah Bin Sina (*Avicenna*), another well-known medical figure during the 11th century, described lemon balm as the ideal medicinal herb for mood (within the book "The Canon of Medicine" and in a paper on mood disorders "al-Adwiya al-Qalbiye").[28,29] It was further acknowledged that lemon balm plays a unique role in positive mood states, and offers a treatment for anxiety-induced palpitation, often being referred to as an "exhilarator of heartache", which may be attributed to its pharmacological properties. Additional neuropsychiatric effects of lemon balm proposed by *Avicenna* include improvements cerebral circulation, the reduction of anxiety-induced palpitations, in addition to displaying of anxiolytic, anti-vasovagal syncope, anti-epileptic and antioxidant properties.[28] It has also been suggested that lemon balm acts as a tonic for all organs. During the 11th century, Abu Rayhan al-Biruni additionally described lemon balm as an exhilarator of heartaches in his book "al-saydala fi al-tibb (Pharmacopoeia of Medicine).[30]

12th Century

During the 12th century, Abu Jaafar Ahmed bin Muhammad bin Said Al-Ghafiqi described lemon balm as a beneficial remedy for melancholic disease and recommended it for the treatment of ischemic stroke, sadness, mood enhancing and vasovagal syncope (Figure 2: book called "Fi al-Adwiya al-Mufrada").[31,32] Furthermore, Abu l-Khayr al-Ishbili described lemon balm as an anti-depressant and inhibitor of heartaches (as described in the book: "Umdat al-Tabib fi maarifat al-nabat li kuli labib").[33,34]

13th Century

Ibn al-Bayṭār, a comprehensive pharmacopoeia of the Middle Ages, has cited the knowledge of previous scientists relating to lemon balm. In addition, he has described his anecdotal observations following the application of lemon balm on neuropsychiatric symptoms. These observations included the inhibition of heartaches, elevation of positive mood states, reduced insomnia, anti-anxiety-induced palpitations, reduction of panic attacks and obsessive disorders, anti-vasovagal syncope, neuroprotection, and stimulation of positive self-talk.[35,36]

14th Century

Al-Chaghmīnī argued that lemon balm has protective effects on the whole nervous system, alongside several applications relating to peripheral neuropathy, such as sciatalgia, radicular lower back pain, and arthroplasty (in his book "Qānūnchah fi al-tibb"). Importantly, specific to neuropsychiatric disorders, Al-Chaghmīnī recommended lemon balm for seizures, litharghous and amnesia.[37]

Discussion

Throughout history, physicians have consistently believed that lemon balm can improve the symptoms of mood disorders, particularly depression and anxiety. The neuropsychiatric effects of lemon balm have been gradually discovered throughout history. Based on studies dating back to before the 1th century, it can be inferred that lemon balm was initially prescribed predominantly for gastrointestinal disorders.[17] During the 2nd century, Galen was the first to propose and record the neuropsychiatric potential of lemon balm.[18] Subsequently, the first manuscripts involving lemon balm were written by Jundishapur physicians.[13,14] For nearly two centuries, anxiety, depression, and obsessive disorders were the most prevalent neuropsychiatric symptoms for which lemon balm interventions were administered. In the 10th century, new neuropsychiatric applications of lemon balm were implemented. During this stage, *Rhazes* suggested lemon balm to have effects on epilepsy and amnesia.[26] This finding was further confirmed by *Haly Abbas*[27] and al-Chaghmīnī during the 13th century.[37] In line with the described physicians across the centuries, lemon balm has been considered by clinicians as an herbal remedy for the treatment of anxiety, depression, and insomnia (Table 1).

Evidence from pre-clinical and clinical studies confirms

Figure 2. Description and applications of Lemon balm according to "Fi al-Adwiya al-mufrada" by Abu Jaafar Ahmed bin Muhammad bin Said Al-Ghafiqi. Available from: https://archive.org/details/McGillLibrary-osl_al-ghafiqi_MS7508-18872/page/n158/mode/2up.

the efficacy of lemon balm on affective disorders. In animal trials, lemon balm has shown similar anti-depressive effects to imipramine in mice.[38] Moreover, lemon balm has demonstrated anti-depressive effects that mimic fluoxetine in rats,[39] and anti-depressive effects that coincide with serotonin-like mechanisms,[40] ultimately initiating anti-depressive and anxiolytic effects in mice.[41,42] In human randomized controlled trials (RCTs), lemon balm has demonstrated the ability to alleviate a series of neuropsychiatric symptoms, predominantly centered around depression and anxiety. Based on these trials, lemon balm interventions exerted the ability to reduce anxiety, depression,[43] insomnia,[44-47] postpartum depression,[48] anxiety induced palpitations,[49] anxiety in cardiovascular disease patients,[50] and healthy participants.[51] (Table 2) Akhoundzadeh *et al*,[52] inspired by the efficacy of lemon balm in treating amnesia, evaluated its effectiveness in Alzheimer's disease and cognitive disorders, revealing potential benefits.

Lemon balm has been ingested across several centuries in various forms, which include direct food sources, decoction, or infusion.[53,54] Researchers have recently preferred to administer lemon balm interventions in the form of aqueous extracts,[10,50,51] hydroalcoholic extracts,[39,42] lyophilized aqueous extract,[49] essence,[45] or purified bioactive substances.[55,56]

The recent evidence-based findings and lengthy history involving the application of lemon balm in neuropsychiatry, have provided vital knowledge in the field of mental health. Future research should aim to draw upon the findings derived across the centuries in addition to more recent studies, to determine the mechanisms of lemon balm and its clinical application in psychiatric medicine. These results could potentially lead to the development of an effective neuropsychiatric remedy.

Conclusion
Historically, lemon balm has been a well-known medicinal herb. The therapeutic effects of lemon balm in the field of neuropsychiatric diseases, specifically depression and

Table 1. Indications and Functions/target symptoms in the use of lemon balm in neuropsychiatric disorders in a number of sourcebooks from the 9th to the 15th century.

Author	Literature	Year (A.D.)	Neuro-psychiatric indications	Functions/target symptoms
Dioscorides	De materia medica	40-90	Not specified	Gastrointestinal symptoms
Galen	-	129-210		Neuro-psychiatric symptoms
Shapur ibn Sahl	Al-adwiya al-murakabba (Aqrabadhin)	Died: 869	Neuropsychiatric symptoms	Not specified
Ali ibn Sahl Rabban al-Tabari	Firdous al-hikmah	838-870	Anxiety-induced palpitation, fear, despondency, faint,	Exhilarator, courage booster
Thābit ibn Qurra	Al-dhakhīrah fī 'ilm al-ṭibb	836-901	Melancholia, sadness, fear, obsessive, panic, low-spirit	Anti-obsessive, anti-psychotic, mood enhancer
Muhammad ibn Zakariya al-Razi (Rhazes)	Al-hawi fi al-tibb Khavas al-ashia Abdal-al-adwiya	865-925	Sadness, severe depression, epilepsy, amnesia, low-spirit	Anti-epileptic, Anti-amnestic
Ali ibn al-Abbas al-Majusi (Haly Abbas)	Kāmil aṣ-ṣināʿa aṭ-ṭibbiyya	Died between 982-994	Sadness, anxiety, low-accuracy, amnesia, headache	Accuracy enhancer, headache analgesic
Avicenna	Canon of medicine al-adwiya al-qalbiye	980-1037	Ischemic stroke, despondency, anxiety-induced palpitation, anxiety, faint, panic, epilepsy,	Ischemic stroke, cerebral circulation improver, tonic for all organs, antioxidant,
Abu Rayhan al-Biruni	Al-saydala fi al-tibb	973-1050	Despondency	Not specified
Abu Jaafar Ahmed bin Muhammad bin Said Al-Ghafiqi	Fi al-adwiya al-mufrada	Died: 1165	Melancholic, ischemic stroke, low-spirit, faint, sadness	Not specified
Abu l-Khayr al-Ishbili	Umdat al-tabib fi ma'arifat al-nabat	1108-1179	Depression, despondency, sadness	Not specified
Ibn al-Bayṭār	Al-jāmiʿ fi al-adwiya al-mufrada	1197-1248	Affective disorders, heartache, sadness, insomnia, panic, obsessive, faint, ischemic stroke, nightmare, self-talk, neurodegeneration, anxiety-induced palpitations,	Hypnotic, neuroprotective
Al-Chaghmīnī	Qānūnchah fi al-tibb	Died 1344	Sciatalgia, radicular lower back pain, arthropathy, seizure, litharghous, amnesia	Peripheral neuropathy remedy

Table 2. Evidence of the effectiveness of Lemon Balm in neuro-psychiatric disorders in recent randomized clinical trials.

Author / year	Neuro-Psychiatric disorders	Lemon Balm efficacy
Scholey et al.[10] 2014	Cognitive impairment and Anxiety	Cognitive and mood performance was improved.
Alijaniha et al.[49] 2015	Anxiety, Depression, Insomnia, Palpitation, Social-dysfunction, Somatization	The number of patients with anxiety and severe depression, was reduced.
Chehroudi et al.[44] 2016	Depression, Anxiety, Insomnia	Anxiety and depression were significantly reduced in patients.
Heydari et al.[45] 2018	Depression, Anxiety, Social disorders, Sleeping-disorders, Somatoform-symptoms	Sleep quality, anxiety disorders and depression were significantly improved.
Haybar et al.[46] 2018	Anxiety, Depression, Stress, Sleep disorders	Depression and anxiety scores decreased significantly.
Beihaghi et al.[48] 2019	Depression (Blues)	The intervention significantly reduced the incidence of postpartum depression in the treatment group.
Lotfi et al.[50] 2019	Anxiety	Anxiety state was significantly improved in the intervention group.
Soltanpour et al.[47] 2019	Anxiety, Sleep-quality	The levels of anxiety and sleep quality in participants improved by 49% and 54% respectively.
Saeidi et al.[51] 2020	Anxiety	Anxiety symptoms were significantly reduced in the intervention groups.
Araj-Khodaei et al.[43] 2020	Depression	Lemon balm was able to improve mild to moderate depression, similar to fluoxetine.

anxiety, have been accentuated by physicians throughout history and are further strengthened by recent studies. Based on the reviewed history, it is anticipated that the long history of lemon balm will prompt future researchers to thoroughly explore the potential of lemon balm in neuropsychiatric disorders.

Author Contributions
JG, MT, AF, RM and MA-K, contributed in conception and data collection of the review. JGH, NT, RM and MA-KH, contributed in manuscript drafting. Manuscript edited by MA-KH, RM and NT. SS-E and SH, contributed in data interpretation and revising of the review. The final version has read, and was confirmed by all authors for submission.

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Conflict of Interest
One of the authors of the article (Sanaz Hamedeyazdan) is the associate editor of the journal. This author was completely excluded from the review process of this article.

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