

Phytotherapeutical implications in pain perception-focusing on schizophrenia

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Abstract

Schizophrenia is an extremely complex psychiatric disease where perception of pain is altered, varying from abolition to lack of any kind of changes compared to normal controls and even hypersensitivity. In this way, the hypothesis of amending schizophrenia through pain therapy enhanced the importance of pain medication. But managing pain phenomenon in schizophrenia has large and unknown implications. Nevertheless, pharmacological interactions between the medications for these two entities are unknown and most likely would have a lot of side-effects and therefore ethnopharmacological methods became once again an interesting option. Traditional medicine wisdom was followed in the pursuit of finding connections between ancient knowledge and current scientific proven facts.

To our best of knowledge, this is the first time when pain, plants and schizophrenia are discussed together. In this way, it seems that by replacing fully synthesized chemical products, the risk of side-effects decreases. Also, it appears that some plants besides treating pain may have curing effects on the psychotic activities in schizophrenia.

Therefore, through this mini-review we emphasized on the advantages of the ethnopharmacological approaches in pain conditions in the context of schizophrenia, but also highlighted some cases of inappropriate usage of plants in traditional therapy.

Keywords: schizophrenia; pain in schizophrenia; "phytotherapy and pain; antinociceptive activity in ethno pharmacology

Introduction

Schizophrenia is a severe disabling mental disorder characterized by impaired cognitive functions and contact with reality. Its symptoms were first described by psychiatrists Morel Benedict and Emil Kraepelin. Later on, Swiss psychiatrist Eugene Bleuler came up with the term schizophrenia to describe the symptoms noticed by Benedict and Kraepelin [1].

Pain with its main features, singularity and subjectivity is a phenomenon hard to describe in all its aspects. Even from the first reports of the schizophrenic disorder the relative insensitivity to pain of patients with schizophrenia was brought to attention [2]. Although, there are not many studies on pain perception in the schizophrenic disorder, most of them advocate for the theory that schizophrenic patients experience abolition or lack of pain perception [3,4,5,6], but opinions are parted in this matter. Despite the belief that schizophrenic patients encounter decreased pain perception, the importance of pain treatment and the necessity of finding an efficient analgetic are backed up by some studies which show amendment of the psychiatric condition once the pain is treated.

In this context, the relevance of natural medicine is obvious considering that it possesses a small number of side effects when using plants in therapy [7]. Therefore, investigating for a new, natural, safe and efficient analgesic is a great challenge and shows promising future for the researcher. Adding up to this challenge is the existence of the psychiatric disease which slows down treatment of pain because of lacking its diagnostic. None the less, foreseeing the future brings us to think about natural ways of treating pain so that interactions with antipsychotic medication can be avoided.

Therefore, in this mini-review we will try to highlight different aspects of the interactions between plants and the human organism, pointing out especially the influence of plants on pain treatment and taking a special interest in schizophrenia.

Materials and methods

The information used for this mini-review was gathered using the main scientific databases (eg Sciencedirect, Scopus, Pubmed, Oxford Journals) from inception until January 2016 using the following keywords "schizophrenia", "pain in schizophrenia", "ethno

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pharmacology of pain”, “antinociceptive activity in ethno pharmacology”. Cross-references for these words were also taken into account. Only papers in English language were of interest. There was conducted an attentive selection of the articles included in this mini-review by their titles and abstracts. After this step, full texts of the remaining publications were evaluated. In this process were involved two separate researchers (I.A. and S.G.) Any contradictory opinions in the matter of selection for this paper were resolved by common consent.

Pain and schizophrenia

Psychiatric disorders represent 13% of all global diseases [8]. One of the most representative mental illnesses is schizophrenia, affecting 1% of the population. This psychiatric condition is accompanied by hallucinations, chaotic thoughts, delusions, cognitive deficits [9].

The old DSM-IV criteria divided schizophrenia in several types: paranoid, catatonic, disorganized, residual. According to the new DSM-V criteria, these types of schizophrenia are not used anymore, having just an historical purpose [10].

The causes of appearance of this disease are not yet clear and are still of great interest in research. There have been made some assumptions regarding the genesis of schizophrenia. One of them is hereditary, another are implications of certain factors in critical moments of brain development. Also certain changes regarding neurotransmitters and other factors are involved. Some hypothesize that a genetic component is related to the appearance of schizophrenia disease.

Some researches highlighted that it is a hereditary disease singularized in families where it manifests mostly in twins [11-14]. Pursuing these idea recent studies using new genetic technologies brought a substantial contribution by identifying specific genes associated to the disease and also clearing the genetic architecture of this disorder [15]. Heredity plays an important role considering the risk of manifesting schizophrenia, due to the genetic heritage [12]. Another factor that increases risk of schizophrenia is encountered if during conception the age of the father is elevated [16,17].

Notable in the context of this complex and heterogeneous disorder is the altered pain perception, some schizophrenic patients manifesting insensitivity to pain [2]. Pain is a subjective phenomenon, defined by the International Association for the Study of Pain as being “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” [18]. Because of the individuality and impossibility of quantifying with precision pain experience, arise different situations that can become contradictory. When in this mixture is added a disease that alters the contact with reality, cognitive function and elements that help understanding and perceiving pain, the presence of altered pain perception is no wonder.

Most of the studies affirm that patients with schizophrenia have a high tolerance to painful stimuli. This observation has been made since the disease was diagnosed for the first time by Kraepelin, who reported lack of adaptative reactions to different types of injuries such as burns, pinpricks and others [2,19, 20]. Also, there are other cases cited in literature that involve schizophrenic patients diagnosed with acute appendicitis or perforated bowel who did not declare any sort of pain [3, 4, 6] or complained of a mild or intermittent pain, but without the presence of hard abdomen [5,6]. Although there are studies that prove the absence of any differences between normal group and schizophrenic patients [21], Strassnig and collaborators claim that people suffering from schizophrenia feel pain at a higher level [22,23]. Another research that sustains the Strassnig hypothesis is made by Girard and collaborators who tested tolerance to pain in similar medical conditions and noticed hypersensitivity to pain in schizophrenic patients [24,25].

Consequently, taking into account all the research regarding pain in schizophrenia one thing is certain, altered pain perception is a fact in schizophrenic disorder [26].

In particular, of extreme importance in medical practice is determining pain perception in patients suffering from schizophrenia, as they are exposed to higher risks of experiencing other illnesses that develop together with the psychiatric disorder [23, 27-30] and can put in danger the life of the patient. Also, chronic pain is considered to be a factor of great importance in the evolution of the psychiatric disease, treating pain leading to a possible regression of schizophrenia [31]. Therefore, treatment of pain in schizophrenia is a priority and a necessity.

Plants and pain

A substantial interest was manifested in the past towards bioactive components from medicinal plants that can amend symptoms from various diseases. Today, the importance of phytotherapy comes back into attention, being exploited the potential of plants and their effectiveness in curing or decreasing pain phenomenon that can cause aside from the flagrant physical and psychological discomfort, worsening symptoms in the context of schizophrenia

Taiwe and Kuete emphasize on the utility of some specific plant therapies with certain plant species in the treatment of disorders such as anxiety, convulsions, dizziness, headache, insomnia, migraine, restlessness, pain and schizophrenia [32]. Along these lines the interaction between vegetal component and human is used with the purpose of amending or even treating several deficiencies in the human body, including pain phenomenon.

Following the same principle, the use of several plants in traditional medicine for treating painful experiences is being tested for its accuracy by extracting the active components and testing them on animal models so that their effects can be observed.

Literature has a great collection of researches made on plants and their effects on pain perception; recently a growing interest on this



matter has been noticed. In effect, Imam and Moniruzzaman researched the antinociceptive effect of ethanolic extract from *Lannea coromandelica* leaves, belonging to the family *Anacardiaceae* [33]. This is a small tree with falling leaves that is cropped especially for its ornamental proprieties, being used as a live fence. Different parts of this plant are utilized by traditional medicine in Bangladesh for treating a large number of affections. According to Zheng and Xing, the leave of the plant is used in the treatment of wounds and hematochezia (fresh blood found in or with stools) [34]. Another area where branches of this plant find use is oral hygiene as toothpicks. In addition, the bark of the tree is considered efficient in skin disease treatment, leaves and root consumption is registered in stomach aches [35]. Also, leaves decoction is applied on local swellings and painful places [36, 37]. Furthermore, the bark of this tree has many applications being used in numerous illnesses such as dyspepsia, gout, dysentery [38], bruises, injuries, burns, ulcers, dry eyes, swellings and bodily pain [39], also skin eruptions, teeth aches [42]. Based on the large usage of this plant in different treatments, Imam and Moniruzzaman tested the antinociceptive effect of ethanolic extract from leaves of *L. coromandelica* using pain animal models. Different doses were tested on pain animal models induced using thermal or chemical stimuli. It turned out that the antinociceptive effect is dependent on the dosage in both models of induced pain. Altogether, this study confirms and approves of the treatment direction in which this plant was valued in traditional medicine [33].

Another research conducted by Khan and collaborators, follows the antinociceptive activity in pain animal models of the *Polygonatum verticillatum* rhizomes. *Polygonatum* genus consists of 57 species belonging to Liliaceae or Convallariaceae family. It is considered to be widespread in East Asia, especially in China and Japan where 40 *Polygonatum* species can be found [40,41], but it is also found in large sections of Europe. *Polygonatum verticillatum* is a perennial rhizomatous herb [42] from which fresh rhizomes syrup is employed valued against pain, stinging sensation, fever and tuberculosis [43]. This herb has also a diuretic effect along with reducing burning sensation during urinating when it is combined with other herbs [44]. Khan et al. research made on Whorled Solomon's-seal (folk term for *Polygonatum verticillatum*) is designed to establish if its traditional usage is correct. Different doses of raw methanolic extract of rhizomes of *Polygonatum verticillatum* were tested on pain models in rats utilizing writhes induced by acetic acid-equivalent of visceral pain, formalin test, which reproduces inflammatory pain, hot plate test recording spinal and suprapinal nociception. In the final analysis, Khan's group experiment proves the existence of mechanisms that confirm the analgesic proprieties of *Polygonatum verticillatum* rhizomes. On the contrary, the diuretic proprieties were not evidenced, presenting statistically insignificant diuretic proprieties [42].

Another study that comes to back-up traditional knowledge is made by Uddin and collaborators where extracts and chemical constituent of *Diospyros lotus* L were researched. The plant involved in Uddin et al experiment is a perennial tree belonging to

the Ebenaceae family, widespread in China, Asia and southeast Europe. The purpose of Uddin et al study was to verify the traditional belief that this plant possesses anti-nociceptive, anti-inflammatory and sedative effects. Anterior researches indicate that *D. lotus* fruits have sedative, astringent, nutritive, antiseptic, anti diabetic, antipyretic, laxative, antineoplastic effects [45,46]. Adding to the former knowledge on this plant its fruits are encountered in the treatment of diarrhea, dry cough, hypertension [47]. Based on these conditions, Uddin et al research studied the effect of chloroform fraction and some isolated compounds (diospyrin and 8-hydroxysodiospyrin) in *Diospyros lotus*, using known pain animal models [48]. Overall, the chloroform fraction, diospyrin and 8-hydroxysodiospyrin attested pronounced anti-nociceptive, anti-inflammatory and sedative effect, therefore acknowledging its traditional usage.

To emphasize on the potential of natural compounds, another research highlights the probable analgesic, anti-inflammatory and antioxidant effects that the hydroalcoholic extract of *Areca catechu* L. nut possesses. Already knowing that a compound named arecoline isolated from *Areca catechu* has important dose-dependent antinociceptive activity [49], it was followed if hydroalcoholic extract of the same plant expresses analgesic, anti-inflammatory and antioxidant potentials [50].

For this reason, the parameters trailed in animal models were the analgesic activity through hot plate test and formalin-induced pain in mice, the anti-inflammatory activity caused by carageenan-induced edema in hind paws of rats and in vitro antioxidant activity. In the final analysis, in both analgesic tests there were reported high levels of analgetic potency of the hydroalcoholic extract and a dose-dependent anti-inflammatory effect. Also, in vitro testing of the antioxidant activity showed a positive effect in this area, as well, proving to carry good antioxidant proprieties [50].

Summarizing, this traditional medicinal plant adopted in multiple therapies such as antihypertensive [51], hypoglycemic [52], wound healing [53], anti-HIV [54], antidepressant [55], antihelminthic and aphrodisiac [56], also indicated in diarrhea, urinary disorders and skin disorders [57], it has proven its analgesic, anti-inflammatory and antioxidant capacities [50].

Besides the studies mentioned above, there are a lot others that approve of the traditional medical practices, arguing their perspectives through testing the effects of the plants used. It is worth reminding here the researches made on the antinociceptive effects of plant extracts such as *Phyllanthus fraternus* family Euphorbiaceae, with proven action on chronic pain induced in mice showing a potential worth mentioning in managing persistent pain [58]; *Rourea induta* Planch family Connaraceae – aqueous extract from leaves - proven high effectiveness in antinociceptive action, approving of previous phytotherapeutic use [59]; *Pistacia integerrima* family Anacardiaceae – the pistagremic acid isolated from this plant shows a strong peripheral as well as central antinociceptive activity, presenting also antiinflammatory and antipyretic qualities [60]; *Xeromphis nilotica* family Rubiaceae – aqueous extract from root bark –has a short antiinflammatory



quality and an antinociceptive effect [61]; *Impatiens balsamina* family **Balsaminaceae** – flower methanol extract – central and peripheral antinociceptive properties are reported [62]; *Geoffroea decorticans* family **Fabaceae** – aqueous extract from fruits and syrup- own significant antinociceptive effects [63]; *Remirea maritime* family **Cyperaceae** – aqueous extract from this plant indicates analgesic properties in different experimental pain models, leading to the assumption that they manifest due to the inhibition of peripheral mediators which could be related to the powerful antioxidant effects noticed *in vitro* [64]. All of the above are sustaining custom plant treatment.

Even if there are a large number of studies that confirm traditional plant therapy as being correctly applied, the result must not be generalized. The research carried by Taiwe and Kuete comes to deny many traditional plant therapies, some having opposite effects to the ones they were used for. As a repercussion, behind the degenerative disease widespread in some tropical areas known as ataxic neuropathy stands chronic usage of some neurotoxic plants in the diet. Other effects encountered as a result of the consumption of plants in traditional medicine containing chemical substances with interesting pharmacological effects are delirium, panic and sometimes profound coma [32]. Some examples of these plants used in traditional medicine causing neurotoxicity are *Solanum kwebense* (**Solanaceae**) encountered in treatment of abdominal pain, inflammation and rheumatism, offers instead cerebellar cortical substance degeneration, involving selectively Purkinje neurons [65]. Another example is *Nicotiana glauca* (**Solanaceae**) recommended traditionally for treatment of dizziness, migraines and headaches, has as secondary effects convulsions, dyspnea and hallucinations [65,66]. Although it has degenerative effect through growth of lysosomal activity, *Manihot esculenta* Crantz (**Euphorbiaceae**) is indicated by traditional African medicine in treatment of Ringworm, tumor, conjunctivitis, sores and abscesses, inflammation. The list of examples can go on, which brings us in sight the necessity of testing every type of plant used in traditional medicine so its secondary effects can be followed or to verify the rightfulness of the choice made for the treatment of the diagnosed illness.

Schizophrenia, pain and plants

We must not forget that schizophrenic disorder causes altered pain perception, although there are some reports that state no difference of perception between healthy controls and schizophrenic patients. Emphasizing on pain perception in these patients is crucial considering that besides the fact that it causes an impediment in developing normal activity it has an impact on the evolution of the psychiatric disease [31].

In this, context a different route for this matter can be represented by reaching schizophrenia and pain through traditional plants. In this way, in the framework of phytotherapeutical approaches it is also considered the possibility of treating schizophrenic

manifestations using active principles from plants. Moreover, the discovery of a plant that could have positive effects on both pain and schizophrenia would be ideal having in mind that natural solutions come with less side-effect compared to synthetic ones.

Although the aforementioned idea would revolutionize the treatments in both conditions and cut back many of the undesired effects of the current used medication, there are not many inquires made in this field.

One example in this matter has been made on *Cannabis sativa*, a plant that has a long historical use for its pain-relieving qualities, but because of its hallucinogen properties has been restricted in use [67], lately regains its forgotten importance in the researches following pain treatment. Already famous for its analgesic properties, even recent studies demonstrating that its psychoinactive component, cannabidiol (CBD) has possible positive effects on neuropathic pain [68] also shows potential in treating psychotic symptomatology, CBD looking to carry a pharmacological profile comparable to that of an atypical antipsychotic [69]. From the compounds belonging to *C. Sativa*, cannabinoids are the most representative ones and possess proven efficacy in the treatment of neuropathic pain [70], but their area of pain treatment is larger including cancer pain [71], rheumatoid arthritis [72], improves spasticity in MS patients [73] and also might be an answer to neuropathic orofacial pain [70]. Evidence suggests the possibility that cannabidiol the non-psychoactive component of *C. Sativa*, also plays a role of relief in inflammatory pain, reversing thermal and mechanical hyperalgesia induced in inflammatory pain animal models [68].

In this context, given the famous properties of cannabis with regard to its capacity of inducing psychoactive effects which resemble to the ones met in schizophrenia [74] and the fact that McDonough team demonstrated its possible importance in pain perception [70], then we can speculate that using this plant in the management of pain in schizophrenia would be of great help.

A crucial aspect of schizophrenic population is the exposure to high risk of encountering physical diseases [27] that are the source of potential pain phenomenon. One of the conditions that has increased occurrence in schizophrenic disorder and that raises pain experiences encounters is irritable bowel syndrome [75]. There is evidence that this CBD, extracted from *Cannabis sativa* plant and also cannabigerol (CBG) extracted from the same plant could be used in the treatment of intestinal inflammation [76,77] and therefore in reducing pain phenomenon caused by this pathology. In addition, our group is also interested in testing pain perception in a rat model of irritable bowel syndrome, and is currently working on a special model of restraint stress-induced intestinal deficits [78] in pain perception and negative symptoms similar to the ones encountered in schizophrenia.

Currently the utilization of *C. Sativa* in therapy has a long history and some of the drugs found in clinic at the moment, containing cannabis based compounds are Cesamet® (Nabilone, Meda Pharmaceuticals, Somerset, New Jersey, USA), Marinol® (Dronabinol, Abbvie Inc., North Chicago, ILN, USA), Sativex® (GW



Pharmaceuticals, Salisbury, UK) (70). In detail Cesamet® (Nabilone, Meda Pharmaceuticals, Somerset, New Jersey, USA) and Marinol® (Dronabinol, Abbvie Inc., North Chicago, ILN, USA) incorporate synthetic derivative of the plant cannabinoid tetrahydrocannabinol (THC), both of them holding pain relief capacities, one of them showing efficiency in chronic neuropathic pain [79], the other demonstrating analgesic competency [80]. At the same time, a tolerance/dependence statistic has not been assessed for Cesamet® (Nabilone, Meda Pharmaceuticals, Somerset, New Jersey, USA) and regarding Marinol® (Dronabinol, Abbvie Inc., North Chicago, ILN, USA), new evidence suggests the presence of a psychoactive effect resembling the one met in cannabis use if utilized in the treatment of chronic non-cancer pain patients [81]. On the other hand, Sativex® (GW Pharmaceuticals, Salisbury, UK) composed by plant-derived cannabinoids THC and cannabidiol provided analgesic reaction to cancer pain [71] and to neuropathic pain encountered in MS [82], even ameliorating long-term spasticity in MS patients [73].

Considering the analgesic effect that Sativex® (GW Pharmaceuticals, Salisbury, UK) manifests over cancer pain and knowing that in the case of schizophrenia there is encountered a high rate of cancer occurrence [83,84,85], it can be speculated that the cannabinoid compound might also ameliorate or cure pain in the context of schizophrenia.

This recent finding stating that cannabidiol (CBD), a constituent of *Cannabis sativa* may have antipsychotic effect [86] brings a new vision in the matter of severe mental illness treatment. On the other hand it has been accepted that cannabis use is associated with potential schizophrenia outcomes due to 9-tetrahydrocannabinol (THC), component with psychotic proprieties [87]. But not all individuals are exposed, several factors have been proposed to increase the risk of schizophrenia in cannabis users and these are: dose-related relationship explained as the degree of exposure to cannabis, genetic predisposition, other environmental risk factors and the age of first exposure to cannabis [87]. Although, THC has psychotic effects another component CBD, appears to have reverse effect, even being considered for treatment of psychotic episodes such as the ones encountered in schizophrenia. The proof of its propriety is brought by experiments made on animals but also on humans [86]. It has been demonstrated that CBD can decrease symptoms triggered by afore use of THC, in particular anxiety [88]. Some argue for CBS's effect against THC even if it is administered before THC, others deny this fact [89,90].

From clinical studies it can be seen that CBD has similar effects to antipsychotics, but with the advantage of flagrant fewer side effects concerning extrapyramidal effects, prolactin increase, weight gain [91].

As former knowledge indicates, usage of antipsychotics in treatment of schizophrenia has been known to also ameliorate pain [92], but it remains to be studied, first if CBD can be used as an antipsychotic, though evidence suggests its effectiveness and diminished to lack of repercussions, second if it has the same analgesic effects as some antipsychotics are known to possess,

but as aforementioned studies illustrate it might have a real good analgesic potential. Adding up CBD's antipsychotic proprieties and evidence of use in pain therapy makes this compound into the perfect candidate to treat pain in schizophrenia and also schizophrenia itself without expressing the same amount of side-effects as antipsychotics used nowadays.

Furthermore, the search for new analgesics is far from over considering the multiple side-effects that the current synthetic ones imply and their inconstant effectiveness. This is why attention has been cast again on natural solutions to these problems, recalling that different plants were used in the past in pain relieving treatment by traditional medicine employing the opioid system. In this way dehydrocorybulbine (DHCB), purified from *Corydalis yanhusuo*, a plant used in traditional Chinese medicine, has shown antinociceptive effect, inflammatory pain relief and amendment of injury-induced neuropathic pain in pain animal models. Another aspect worth mentioning is that phenomenon of antinociceptive tolerance have not been registered [93]. Also, it was noticed that DHCB at non-sedative doses has similar analgesic response as the one obtained when using high doses of morphine [93].

Acknowledging that *C. Yanhusuo* is from Papaveraceae family, the same family as opium (*Papaver somniferum*), it may express its activity on opioid receptors [93]. Adding up to this context, there is evidence suggesting the existence of a connection between endogenous opioidergic system and schizophrenic disease [94], emphasized on by the psychotic activity that showed by plants dependent on the opioid receptors. For example, the decoction of seed capsule of *Papaver rhoeas L.* has been traditionally used for its narcotic and sedative effects [93], also Papaveraceae plants are effective in treating conditions like insomnia, reducing inflammation and several compounds present antidepressant, antimicrobial and anti-inflammatory activities [95].

Therefore, under these circumstances, bearing in mind the effect against pain and the link with schizophrenia that these opioid pathways have, arises the hypothesis that both pain perception and schizophrenic symptoms could be controlled through a specific modulation of the opioid system.

Moreover, an interesting connection between cannabinoids and opioids has been recently highlighted, that might open new opportunities in the treatment of neuropathic pain and in the development of new analgesics. There has been emphasized on the synergism between the cannabinoid-opioid receptor systems, showing that low doses of cannabinoid agonists combined with opioid agonist have a promising outcome [96]. Although, tolerance and cross-tolerance must not be ignored, occurrence of addiction phenomenon is another impediment adding to their limiting usage on the long run [96].

In effect, strategies have been developed in order to reduce the side-effects encountered. Thus, they propose combining opioid and cannabinoid agonists or targeting receptor heteromers directly. These new ideas are in need of exploration, but show promising potential in diminishing chronic pain [96], representing a starting point in the new avenue unfolding in the story of pain treatment.



Considering that pain pathways share common grounds with some psychiatric pathologies one of them being schizophrenia, there might be developed new approaches in treating pain encountered in complex severe psychiatric disorders such as schizophrenia, but also ameliorate schizophrenic specific symptoms through analgesic treatment of chronic pain [31].

Our team also aims to research this new avenue that expands its course engaging in a fascinating new journey of links between the

two systems cannabinoid and opioid that modulated the activity of one another. Adding up to this idea is the unique perspective of multiple effects of the same compound, extracted from the ancient known *Cannabis sativa* that has effect on pain perception and as well proved efficacy as antipsychotic. Because current results are in need of confirmation we are eager to engage in this controversial research. We present below several plants relevant for pain and/or schizophrenia in the table below.

Plant and Family	Analgesic effect	Antipsychotic effect	Other effects	Traditional medicine usage
<i>Areca catechu L nut</i> (Areaceae)	hydroalcoholic extract – antinociceptive effect [50]	-	hydroalcoholic extract – anti inflammatory, antioxidant effects [50]	Antihypertensive [51], hypoglycaemic [52], wound healing [53], anti-HIV [54], antidepressant [55], antihelminthic, aphrodisiac [56], treatment of diarrhea, urinary disorders and skin disorders [57]
<i>Cannabis sativa</i> (Cannabaceae)	cannabidiol (CBD) – neuropathic pain [68,70], inflammatory pain [68], cancer pain [71]; cannabigerol (CBG) -intestinal inflammation pain [76,77]; cannabinoids - cancer pain [71], rheumatoid arthritis pain [72], neuropathic orofacial pain [70]; THC(⁹ -tetrahydrocannabidiol) – cancer pain [71]	CBD - Pharmacological profile similar to atypical antipsychotic [69], antipsychotic effect (86)	hallucinogen properties [67]; ⁹ -tetrahydrocannabidiol (THC) - potential schizophrenia outcomes [87]; cannabinoids – improves spasticity in MS patients [73]; CBD - treatment of intestinal inflammation [76, 77]	diuretic, anti-emetic, anti-epileptic, anti-inflammatory, painkilling and antipyretic properties [97]
<i>Corydalis yanhuso</i> (Papaveraceae)	Antinociceptive effect in pain animal models, inflammatory pain relief amendment of neuropathic pain [93]	-	anxiolytic properties [98]; primary dysmenorrhea [99]; improve the efficacy of chemotherapy [100]; extract - attenuated cardiac hypertrophy [101];	treatment of various pains [98], insomnia, reducing inflammation and several compounds present antidepressant, antimicrobial and anti-inflammatory activities [95], sedative, and hypnotic properties [98]
<i>Diospyros lotus L</i> (Ebenaceae)	chloroform fraction and some isolated compounds (diospyrin and 8-hydroxysodiospyrin)- antinociceptive effect on animal models [48]	-	chloroform fraction and some isolated compounds (diospyrin and 8-hydroxysodiospyrin) – anti –inflammatory, sedative effect [48] fruits- sedative, astringent, nutritive, antiseptic, antidiabetic, antipyretic, laxative antineoplastic effects [45, 46]	Fruits – treatment of diarrhea, dry cough, hypertension [47]



<i>Geoffroea decorticans</i> (Fabaceae)	aqueous extract from fruits and syrup- antinociceptive effects [63]	-	stem barks and aerial parts - antifungal properties [102, 103];	fruits - culinary and medicinal purposes [104]; treatment of inflammatory diseases of the respiratory system, like bronchitis, laryngitis, pharyngitis [63] ; barks, leaves, flowers and fruits - antiasthmatic, emollient and antitusive [105].
<i>Impatiens balsamina</i> (Balsaminaceae)	flower methanol extract – central and peripheral antinociceptive proprieties [62]	-	petal extract – antianaphylactic [106], antipruritic, and antidermatitic effect [107], anti- microbial activity [108]; seeds -antimicrobial activity [109]	thorn or glass-puncture wounds, abscesses [108], scrofulosis, carbuncles, dysentery [110], rheumatism, isthmus, crural aches, fractures, superficial infections, fingernail inflammation [111], tumor, difficult labor, puerperal pain [112], emetic, cathartic, diuretic, for pain in the joints [113]; aerial parts – treatment of articular rheumatism, bruises, beriberi [106]; flowers-lumbago, neuralgia, burns, scalds treatment [113]; juice of petals – topical skin application to treat dermatitis including urticaria [106].
<i>Lanea coromandelica</i> (Anacardiaceae)	ethanolic extract from leaves - antinociceptive effect in animal models of pain [33]; bark - analgesic activity [114].	-	bark - anti-inflammatory proprieties [39], hypotensive [115], antihyperglycemic [116], wound healing, antimicrobial [117], antioxidant [114]; leaf extract – antidiarrhoeal [118], anti-inflammatory activity [119].	leaves-treatment of wounds and hematochezia [34]; branches – oral hygiene as tooth picks; bark of the tree - skin diseases, dyspepsia, gout, dysentery [38], bruises, injuries, burns, ulcers, dry eyes, swellings and bodily pain [39], skin eruptions, teeth aches [42]; leaves and root – stomach aches [35]; leaves decoction – local swellings and painful places [36, 37]
<i>Manihot esculenta</i> Crantz (Euphorbiaceae)	-	-	degenerative effect through growth of lysosomal activity [65]	treatment of ringworm, tumor, conjunctivitis, sores and abscesses, inflammation [32]
<i>Nicotiana glauca</i> (Solanaceae)	-	-	convulsions, dyspnea and hallucinations [66, 65]	treatment of dizziness, migraines and headaches [32]



<i>Pistacia integerrima</i> (Anacardiaceae)	Pistagremic acid – strong peripheral and central antinociceptive activity (60)	-	Antiinflammatory and antipyretic qualities [60]	anti-inflammatory, analgesic, blood purifier, remedy for gastrointestinal disorders, expectorant, anti-asthmatic, antipyretic, antiemetic and antidiarrheal [120,121]; galls- for asthma, diarrhea, chronic bronchitis, disorders of respiratory tract, skin diseases, psoriasis, fever, appetizer, hepatitis, liver disorders, oxidative stress, counter hyperuricemia [121, 122].
<i>Phyllanthus fraternus</i> (Euphorbiaceae)	Plant extracts – chronic pain [58]	-	Aqueous extract – enhance therapeutic potential of anticancer drugs [123], antihepatotoxin, antiviralagent [58], against nephrotoxicity induced by bromobenzene [124]	Liver diseases [125, 126]; management of painful disorders [127]
<i>Polygonatum verticillatum</i> (Liliaceae or Convallariaceae)	raw methanolic extract of rhizomes – analgesic effect on animal models [42]	-	diuretic effect – statistically insignificant [42]	Fresh rhizomes syrup – against pain, stinging sensation, fever, tuberculosis [43]; diuretic effect, reducing burning sensation during urinating when combined with other herbs [44]
<i>Remirea maritime</i> (Cyperaceae)	aqueous extract – analgesic proprieties in different experimental pain models [64]	-	plant extract - antimicrobial, anti-inflammatory proprieties [128, 129].	treatment of diarrhea, kidney disease, fever, pain, inflammations [130]
<i>Rourea induta Planch</i> (Connaraceae)	Aqueous extract from leaves – antinociceptive actions [59]	-	leaf ethanolic extract - in vitro antioxidant activity associated to in vivo hepatoprotective potential [131, 132,133]	treatment of rheumatism and Chagas disease [134]
<i>Solanum kwebense</i> (Solanaceae)	-	-	cerebellar cortical substance degeneration, involving selectively Purkinje neurons [65]	abdominal pain, inflammation and rheumatism [32]
<i>Xeromohis nilotica</i> (Rubiaceae)	aqueous extract from root bark –antinociceptive effect [61]	-	aqueous extract from root bark– short anti-inflammatory quality [61]; rootbark extracts - sedative activities [135, 136]; antischistosomal [137], molluscidal [138] activities	pain, fever, epilepsy and mental disorder [139, 140]



Consequently, if we take into consideration that synergism between cannabinoids and opioids modulates performance in the fight against pain by targeting multiple pain mechanisms and also the aforementioned antipsychotic and antinociceptive properties of cannabidiol and the involvement of opioid mechanisms in pain and schizophrenia, we might be looking at the beginning of a new era in the treatment of pain, but also in the battle against schizophrenia, this complex severe mental illness with modified perception of pain.

Conclusions

The pain phenomenon's phytotherapeutic treatment is still incompletely elucidated and adding into context schizophrenia it makes recognition and treatment of pain even harder. Thus, appears the necessity of finding new methods of pain treatment which can lead to discovering new pathways implicated in the transmission, reception and perception of the algic component. Considering all these aspects, we can speculate that these findings

in pain treatment could even be helpful in the further treatment avenues of schizophrenia.

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Conflict of interest

The authors have no conflict of interest to declare.

Author's contributions

All authors had similar contributions regarding the manuscript writing, literature research, review design, literature analysis and final text approval.

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