

LC – MS Based Quantification Of kyneurinic Acid In Camelliasinensis Extract As A Nutraceutical Treatment In Schizophrenia, Futuristicstudy

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ABSTRACT:

Schizophrenia is a serious mental disorder in which people interpret reality abnormally. It is combination of hallucinations, delusions and extremely disorder thinking highly correlated with depression. The aim of the study is 1. to deprive the depression using nutraceuticals supplements 2. to take treatment which balances the need of the body mode ruling out a regular consumption of medicine through out the life. Kyneurinic acid plays a major role in schizophrenia. During schizophrenia, the kyneurinic acid level is deprived where quinolinic acid level increased. The present study retaining of kyneurinic acid level of consumption if Tea extract. To justify the presence of kyneurinic acid in tea, LC-MS isolation & identification of kyneurinic acid in tea extract is performed. It shows pure tea extract as a promising nutrient supplement increasing the kyneurinic acid level, which is a futuristic study in treating schizophrenia.

KEYWORDS:

Kyneurinic acid, Schizophrenia, Tea extract, Quinolinic acid, depression, hallucinations.

I. AIM & OBJECTIVE

AIM :

To identify and isolate the concentration of kyneurinic acid in Camellia – sinensis (pureh – Tea extract)

To analyse the possibilities of consuming pureh – Tea extract and its beneficiary in treating schizophrenia.

OBJECTIVE:

To quantify the concentration of kyneurinic acid in camellia sinensis.

To analyse the role of kyneurinic acid imbalance and futuristic hope of pureh-tea extract in schizophrenia.

II. REVIEW OF LITERATURE

TEA :

Priya Chaudhry et al stated that, Camellia sinensis plant provides a wide diversity of black, green, oolong, yellow, brick dark, and white tea. Tea is one of the majorly used beverages across the globe, succeeds only in the water for fitness and pleasure.

Job Harenbergetal, reviewed that, Camellia sinensis (green tea) contains caffeine and antioxidant polyphenols. It has been touted as being useful in a wide variety of conditions, including cancer prevention, mostly on relatively slim epidemiological evidence, cardiovascular disorders, and AIDS.

The main adverse reactions to green tea are those of caffeine (qv), with tremulousness and insomnia and withdrawal symptoms (headache, drowsiness, and fatigue).

SCHIZOPRENIA :

D.Jones et.al stated that Schizophrenia is a mental disorder characterized by continuous or relapsing episodes of psychosis. Major symptoms include hallucinations (typically hearing voices), delusions and disorganized thinking associated with depression. Other symptoms include social withdrawal and flat affect. Symptoms typically develop gradually, begin during young adulthood, and in many cases are never resolved. There is no objective diagnostic test; diagnosis is based on observed behavior, a psychiatric history that includes the person's reported experiences, and reports of others familiar with the person. For a diagnosis of schizophrenia, the described symptoms need to have been present for at least six months (according to the DSM-5) or one month (according to the ICD-11). Many people with schizophrenia have other mental disorders, especially substance use disorders, depressive

disorders, anxiety disorders and obsessive-compulsive disorder.

About 0.3% to 0.7% of people are diagnosed with schizophrenia during their lifetime. In 2017, there were an estimated 1.1 million new cases and in 2022 a total of 24 million cases globally. Males are more often affected and on average have an earlier onset than females. The causes of schizophrenia may include genetic and environmental factors. Genetic factors include a variety of common and rare genetic variants. Possible environmental factors include being raised in a city, childhood adversity, cannabis use during adolescence, infections, the age of a person's mother or father, and poor nutrition during pregnancy.

About half of those diagnosed with schizophrenia will have a significant improvement over the long term with no further relapses, and a small proportion of these will recover completely. The other half will have a lifelong impairment. In severe cases, people may be admitted to hospitals. Social problems such as long-term unemployment, poverty, homelessness, exploitation and victimization are commonly correlated with schizophrenia. Compared to the general population, people with schizophrenia have a higher suicide rate (about 5% overall) and more physical health problems, leading to an average decrease in life expectancy by 20 to 28 years. In 2015, an estimated 17,000 deaths were linked to schizophrenia

The mainstay of treatment is antipsychotic medication, along with counseling, job training and social rehabilitation. Up to a third of people do not respond to initial antipsychotics, in which case clozapine may be used. In a network comparative meta-analysis of 15 antipsychotic drugs, clozapine was significantly more effective than all other drugs, although clozapine's heavily multimodal action may cause more side effects. In situations where doctors judge that there is a risk of harm to self or others, they may impose short involuntary hospitalization. Long-term hospitalization is used on a small number of people with severe schizophrenia. In some countries where supportive services are limited or unavailable, long-term hospital stays are more common.

KYNEURINIC ACID :

Sharma k.p.et.al stated that Kynurenic acid (KYNA) is an endogenous antagonist of N-methyl-D-aspartate and $\alpha 7$ nicotinic acetylcholine receptors that is derived from astrocytes as part of the kynurenine pathway of tryptophan degradation.

Evidence suggests that abnormal KYNA levels are involved in the pathophysiology of schizophrenia. However, this has never been assessed through a meta-analysis. A literature search was conducted through Ovid using Embase, Medline, and PsycINFO databases with the search terms: (kynuren* or KYNA) and (schizophreni* or psychosis). English language studies measuring KYNA levels using any method in patients with schizophrenia and healthy controls (HCs) were identified. Standardized mean differences (SMDs) were calculated to determine differences in KYNA levels between groups. Subgroup analyses were separately performed for nonoverlapping participant samples, KYNA measurement techniques, and KYNA sample source. The influences of patients' age, antipsychotic status (%medicated), and sex (%male) on study SMDs were assessed through a meta-regression. Thirteen studies were deemed eligible for inclusion in the meta-analysis. In the main analysis, KYNA levels were elevated in the patient group. Subgroup analyses demonstrated that KYNA levels were increased in nonoverlapping participant samples, and centrally (cerebrospinal fluid and brain tissue) but not peripherally. Patients' age, %medicated, and %male were each positively associated with study SMDs. Overall, KYNA levels are increased in patients with schizophrenia, specifically within the central nervous system. An improved understanding of KYNA in patients with schizophrenia may contribute to the development of novel diagnostic approaches and therapeutic strategies.

DEPRESSION :

George k.g. et al stated that Depression is a syndrome characterized by deep sadness and the inhibition of psychic functions, sometimes accompanied by neurovegetative disorders, with symptoms of anxiety almost always present. The disease produces alterations in a variety of neural networks and neurotransmission systems, along with a dysfunction of the hypothalamic-pituitary-adrenal axis, which leads to concomitant alterations in the immunological response. Generally, there is a parallel increase in proinflammatory mediators as well as oxidative and nitrosative damage caused by a reduction of antioxidant defenses. In a previous review, we compiled and examined studies of medicinal plants that had been evaluated in preclinical assays, including existing data on 155 species studied and reported as antidepressants or as sources of active

principles for treating this condition. This review will thus limit its focus to the 95 clinical trials found in PubMed among the 670 articles on antidepressant-like medicinal plants. To this end, we have reviewed the publications cited in the Cochrane Database of Systematic Reviews, PubMed, and the Science Citation Index from 2000 to 2020. Our review emphasizes those species that have demonstrated the greatest pharmacological potential when studied for their antidepressant properties in humans through clinical trials. Saffron, turmeric, St. John's wort, ginkgo, kava, and golden root are the most relevant plants that have provided important evidence for the treatment of depression in clinical trials.

QUINOLINIC ACID :

Karoline et al stated that Tryptophan and its catabolites (TRY CAT s) have been suggested to link peripheral immune system activation and central neurotransmitter abnormalities with relevance to the etio-pathophysiology of schizophrenia (SZ) and major depressive disorder (MDD). The relationship to different psychopathological dimensions within these disorders however remains to be elucidated. We thus investigated potential group differences of tryptophan, kynurenine, kynurenic acid, 3-hydroxy kynurenine and quinolinic acid in the plasma of 19 healthy controls (HC), 45 patients with SZ and 43 patients with MDD and correlated plasma proteins with the "motivation and pleasure" dimension and cognition. After correcting for the covariates age, sex, body mass index, smoking and medication, patients with MDD showed lower kynurenine and 3-hydroxy kynurenine levels compared to HC. Quinolinic acid correlated negatively with composite cognitive score in patients with SZ, indicating that more severe cognitive impairments were associated with increased plasma levels of quinolinic acid. No correlations were found in patients with MDD. These results indicate that MDD and SZ are associated with dysregulation of the kynurenine pathway. Quinolinic acid might be specifically implicated in the pathophysiology of cognitive deficits in patients with SZ. Further studies are needed to determine whether TRY CAT s are causally involved in the etiology of these neuropsychiatric disorders.

Schizophrenia (SZ) and major depressive disorder (MDD) are prevalent neuropsychiatric disorders with high socioeconomic and individual burden^{1,2} Despite their significant contribution to the global burden of disabilities³ our knowledge of

the underlying etio-pathophysiological mechanisms are sparse and as a result, treatment options remain limited. Both SZ and MDD are heterogeneous syndromes consisting of several symptom dimensions While for a long time considered as separate disorders, there is increasing evidence from clinical psychopathology, neuroimaging and genetic studies that there are both different and overlapping features that characterize these disorders⁷. Therefore, detailed psychopathological characterization and comparison of symptom dimensions with potential biological markers is important. Motivational deficits are symptoms of several psychiatric disorders, including SZ and MDD. Apathy, a reduction of motivation and goal-directed behaviours, has been shown to be prevalent in both patients with MDD and SZ. Further, cognitive dysfunction has been consistently described in both patients with SZ and MDD. There is increasing evidence that the immune system plays a major role in neuropsychiatric disorders, including being causally involved in the pathogenesis of the above discussed symptom dimensions. One candidate pathway linking peripheral immune system activation and central neurotransmitter abnormalities involves tryptophan (TRP) and its catabolites (TRY CAT s).

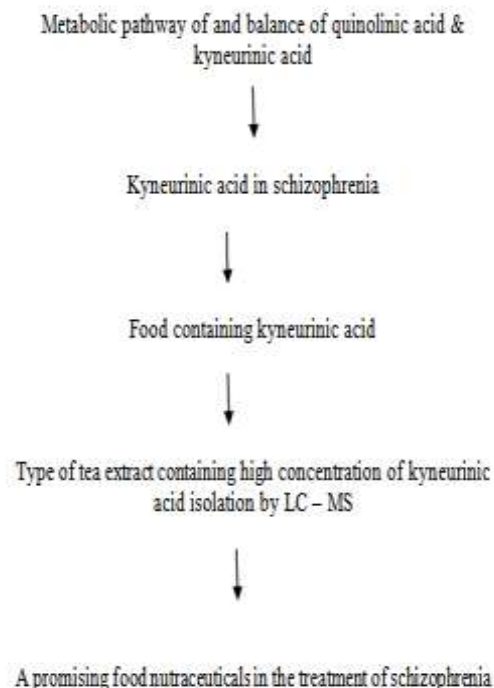
PHARMACOLOGICAL ACTIVITIES :

Coelho et al., 2022, Iqbal et al., 2022, Motyka et al., 2023). Potential green tea catechins mechanisms of action

Sharifi-Rad et al., 2 Apoptosis leads to programmed cell death to remove unwanted or abnormal cells from the body and maintain a stable internal environment

Calina et al., 2020, Calina et al., 2020, Islam et al., 2020, Islam et al., 2021, Salehi et al., 2021). Catechins provide anti-oxidant properties by counteracting the unstable free reactive molecules. Sharifi-Rad et al., 2 Apoptosis leads to programmed cell death to remove unwanted or abnormal cells from the body and maintain a stable internal environment

PLAN OF WORK :



III. INTRODUCTION:

SCHIZOPHRENIA :

Schizophrenia causes psychosis and is associated with considerable disability and may affect all areas of life including personal, family, social, educational, and occupational functioning. Stigma, discrimination, and violation of human rights of people with schizophrenia are common. More than two out of three people with psychosis in the world do not receive specialist mental health care.

A range of effective care options for people with schizophrenia exist and at least one in three people with schizophrenia will be able to fully recover.

Symptoms

Schizophrenia is characterised by significant impairments in the way reality is perceived and changes in behaviour related to: persistent delusions: the person has fixed beliefs that something is true, despite evidence to the contrary; persistent hallucinations: the person may hear, smell, see, touch, or feel things that are not there; experiences of influence, control or passivity: the experience that one's feelings, impulses, actions, or thoughts are not generated by oneself, are being placed in one's mind or withdrawn from one's mind by others, or that one's thoughts are being broadcast to others;

disorganized thinking, which is often observed as jumbled or irrelevant speech; highly disorganised behaviour e.g. the person does things that appear bizarre or purposeless, or the person has unpredictable or inappropriate emotional responses that interfere with their ability to organise their behaviour; "negative symptoms" such as very limited speech, restricted experience and expression of emotions, inability to experience interest or pleasure, and social withdrawal; and/or extreme agitation or slowing of movements, maintenance of unusual postures.

People with schizophrenia often also experience persistent difficulties with their cognitive or thinking skills, such as memory, attention, and problem-solving.

At least one third of people with schizophrenia experiences complete remission of symptoms (1). Some people with schizophrenia experience worsening and remission of symptoms periodically throughout their lives, others a gradual worsening of symptoms over time.

Magnitude and impact

Schizophrenia affects approximately 24 million people or 1 in 300 people (0.32%) worldwide. This rate is 1 in 222 people (0.45%) among adults (2). It is not as common as many other mental disorders. Onset is most often during late adolescence and the twenties, and onset tends to happen earlier among men than among women.

Schizophrenia is frequently associated with significant distress and impairment in personal, family, social, educational, occupational, and other important areas of life.

People with schizophrenia are 2 to 3 times more likely to die early than the general population . This is often due to physical illnesses, such as cardiovascular, metabolic, and infectious diseases.

People with schizophrenia often experience human rights violations both inside mental health institutions and in community settings. Stigma against people with this condition is intense and widespread, causing social exclusion, and impacting their relationships with others, including family and friends. This contributes to discrimination, which in turn can limit access to general health care, education, housing, and employment.

During humanitarian and public health emergencies, extreme stress and fear, breakdown of social supports, isolation and disruption of health-care services and supply of medication can occur. These changes can have an impact on the lives of

people with schizophrenia, such as exacerbation of existing symptoms. During emergencies, people with schizophrenia are more vulnerable than others to various human rights violations, including neglect, abandonment, homelessness, abuse and exclusion.

Causes of schizophrenia

Research has not identified one single cause of schizophrenia. It is thought that an interaction between genes and a range of environmental factors may cause schizophrenia. Psychosocial factors may also affect the onset and course of schizophrenia. Heavy use of cannabis is associated with an elevated risk of the disorder.

KYNEURINIC ACID :

While schizophrenia is characterized by positive, negative, and cognitive symptoms, neurometabolic abnormalities have also been identified as key features of the illness. The longstanding dopamine hypothesis of schizophrenia suggests that dysregulated functioning of the dopaminergic system underlies its pathophysiology. However, the dopamine hypothesis does not readily explain negative and cognitive symptoms. Moreover, a subset of patients (20%–35%) show partial or no response to standard antipsychotic treatments, which exert their effect primarily through dopamine receptor antagonism. Another widely purported pathophysiological mechanism is the glutamatergic hypothesis of schizophrenia. Evidence for this hypothesis arises from pharmacological studies in which N-methyl-D-aspartate receptor (NMDAR) antagonist administration leads to the emergence of positive, negative, and cognitive symptoms in human volunteers. These agents also elicit symptom exacerbation in patients with schizophrenia. Olney and Farber proposed that hypo functioning NMDARs on gamma-aminobutyric acid (GABA)-ergic inhibitory interneurons result in the disinhibition of downstream pyramidal neurons, increasing presynaptic glutamate release within various brain regions. In support, disturbed glutamatergic signaling has been observed in healthy volunteers following acute exposure to an NMDAR antagonist and in patients with schizophrenia. The known effects of exogenous NMDAR antagonists on glutamatergic dysregulation and schizophrenia-like symptomatology have resulted in increased attention towards kynurenic acid (KYNA), the only currently known endogenous NMDAR antagonist.

Kynurenic Pathway KYNA is produced through the kynurenic (KYN) pathway of tryptophan (TRP) degradation, accounting for over 90% of the metabolism of this essential amino acid.²⁹ TRP is oxidized to N-formylkynurenine by 1 of 3 enzymes: indoleamine 2,3-dioxygenase 1 (IDO1), IDO2, or tryptophan 2,3-dioxygenase (TDO2). Next, deformylation of N-formylkynurenine by formamidase produces KYN. KYN is thereafter metabolized through 3 distinct branches of the KYN pathway. KYN can be irreversibly transaminated to KYNA by 4 kynurenic aminotransferases (KATs). KYN can also be oxidized by kynurenic 3-monooxygenase (KMO) to produce 3-hydroxykynurenic (3-HK). Lastly, KYN can undergo oxidative cleavage by kynureninase to form anthranilic acid. The KYN pathway of TRP degradation is initiated by IDO and TDO. These enzymes are known to exist at higher levels in the periphery compared to the central nervous system (CNS). Downstream, KYN readily crosses the blood-brain barrier through the large neutral amino acid transporter; approximately 60% of brain KYN is believed to be contributed from the periphery. In contrast, due to its polar structure, KYNA does not cross the blood-brain barrier. Thus, brain KYNA is predominantly derived from brain KYN. The conversion of KYN to KYNA takes place primarily within astrocytes, as these cells contain KATs but not KMO and therefore cannot degrade KYN to 3-HK and its metabolites. Of the 4 existing KATs, KAT II is thought to be the main enzyme of KYNA production.³⁶ KYNA acts as an antagonist of all 3 ionotropic glutamate receptors, including NMDARs, α -amino-3hydroxy-5-methyl-4-isoxazolepropionic acid receptors, and kainate receptors. However, of these, KYNA preferentially and competitively inhibits the glycine site of the NMDAR. KYNA is also an antagonist of α 7 nicotinic acetylcholine receptors (α 7nAChR); its inhibitory effect on these receptors is achieved noncompetitively through its interaction with an allosteric potentiating site, which is oppositely stimulated by galantamine, an α 7nAChR positive allosteric modulator. KYNA also activates the G-protein-coupled receptor GPR 35 and the aryl hydrocarbon receptor. Additionally, KYNA functions as a free radical scavenger and an antioxidant. Given its capacity to block neuronal excitation and scavenge free radicals, KYNA is widely considered to have neuroprotective and anticonvulsant properties.

KYNA Hypothesis of Schizophrenia The

KYNA hypothesis of schizophrenia posits that disrupted KYNA levels are implicated in the pathophysiology of the illness.⁴⁶ This hypothesis is supported by the notion that KYNA, as an endogenous glutamate receptor antagonist, may mimic schizophrenia-like phenomena induced by exogenous glutamate receptor antagonists, along with evidence from both preclinical and clinical literature.^{41,47,48} Preclinical studies manipulating levels of KYNA have demonstrated its influence on both behavior (eg, cognitive functioning) and neurotransmission (eg, glutamatergic, dopaminergic) observed to be aberrant in patients with schizophrenia.^{41,48} Furthermore, KYNA levels have also been measured in schizophrenia patient populations and deviations from healthy controls (HCs) have often been reported.

QUINOLINIC ACID :

Schizophrenia (SZ) and major depressive disorder (MDD) are prevalent neuropsychiatric disorders with high socioeconomic and individual burden. Despite their significant contribution to the global burden of disabilities³ our knowledge of the underlying etio-pathophysiological mechanisms are sparse and as a result, treatment options remain limited. Both SZ and MDD are heterogeneous syndromes consisting of several symptom dimensions. While for a long time considered as separate disorders, there is increasing evidence from clinical psychopathology, neuroimaging and genetic studies that there are both different and overlapping features that characterize these disorders. Therefore, detailed psychopathological characterization and comparison of symptom dimensions with potential biological markers is important. Motivational deficits are symptoms of several psychiatric disorders, including SZ and MDD⁸. Apathy, a reduction of motivation and goal-directed behaviours, has been shown to be prevalent in both patients with MDD⁹ and SZ¹⁰. Further, cognitive dysfunction has been consistently described in both patients with SZ and MDD. There is increasing evidence that the immune system plays a major role in neuropsychiatric disorders, including being causally involved in the pathogenesis of the above discussed symptom dimensions. One candidate pathway linking peripheral immune system activation and central neurotransmitter abnormalities involves tryptophan (TRP) and its catabolites (TRY CAT s). The essential amino acid TRP is catabolized into several bioactive molecules, including serotonin and products of the

kynurenine pathway. Two enzymes are mainly involved in catabolizing tryptophan to kynurenines: Indoleamine 2,3-dioxygenase (IDO) (which can be indirectly assessed by the tryptophan / kynurenine (KYN) ratio, see below), which in the periphery is mainly present in myeloid cells, and the predominantly hepatic enzyme tryptophan 2,3-dioxygenase (TDO). Upon activation by proinflammatory cytokines such as interleukin (IL)-6, IL-1 β and interferon- γ , TRP is catabolized to kynurenine. Kynurenine can then be catabolized along two pathways: Kynurenine aminotransferases produce kynurenic acid (KYNA) and kynurenine monoxygenase (KMO) converts KYN to 3-hydroxykynurenine (3-OHK), which is further catabolized to quinolinic acid (QUIN). Importantly, KYNA, 3-OHK and QUIN were shown to exhibit neuroactive properties, including affecting glutamatergic, dopaminergic and nicotinic neurotransmission. Evidence for a causal role of kynurenine pathway dysregulation leading to behavioural alterations in several neuropsychiatric disorders comes from animal models, in which it was shown that pharmacologically blocking IDO prevents depression-like behaviours induced by immune stimulation using the bacterial endotoxin Lipopolysaccharide (LPS) or social defeat stress^{19,20}. Several studies have so far investigated group differences in TRY CAT s in the circulation of patients with SZ and MDD, respectively, but have reported inconclusive findings. Recent meta-analyses have shown that KYNA and KYN blood levels were lower in patients with MDD in comparison to healthy controls (HC), while QUIN levels did not differ between the two groups. In SZ, the findings are even more inconclusive: A recent metaanalysis has not found any differences in peripheral KYNA. One large study has found decreased plasma concentrations of 3-OHK in patients with SZ compared to HC, but not other TRY CAT . However, most studies up to date have focused on differences between diagnostic groups rather than correlating TRY CAT s with various symptom dimensions across different diagnoses. The overall hypothesis of the present study was that both MDD and SZ are associated with dysregulation of the kynurenine pathway. Specifically, based on the above discussed literature, we hypothesized that compared to HC, patients with MDD would display lower levels of KYN and KYNA, and patients with SZ would show lower levels of 3-OHK. Based on findings from pre-clinical animal models, we further hypothesized that in both patients with MDD and

SZ, motivational deficits would correlate with the KYN/TRP ratio, as an indicator of IDO activity and the neurotoxic TRY CAT QUIN would be associated with cognitive deficits. Thus, we first investigated group differences in TRY CAT s in the plasma of HC, SZ and MDD subjects and then correlated TRY CAT levels with the psychopathological dimensions “motivation and pleasure” and cognition.

DEPRESSION :

The disease known as depression is a syndrome characterized by profound sadness and the inhibition of psychic functions, sometimes accompanied by neurovegetative symptoms. Unipolar depression is a condition characterized by anhedonia (loss of interest or capacity for pleasure), apathy, changes in sleep and appetite, and sadness; under the worst circumstances, it can also provoke suicidal ideation. Stress is the main trigger of depression as it produces a body's reaction towards a stimulus, displayed in the form of a mental, physical, and/or emotional response. In the latest edition of the DSM-5, the essential core of depression is always characterized by sadness, hopelessness, lack of illusion, and anhedonia, although the clinical picture can be widely heterogeneous in course, intensity, and duration. Due to their high prevalence and long evolution in most cases, diseases such as depression and anxiety require a great number of resources and health expenditure, with economic costs in excess of 200 billion dollars per year. Moreover, depression is the main cause of disability worldwide. The latest report from the WHO points out that globally, 264 million people of all ages are suffering from depression, and 800,000 people die due to suicide every year. Depression is more frequent in women (5.1%) than men (3.6%) and although there are effective treatments for mental disorders, between 76 and 85% of people in low- and middle-income countries receive no treatment for their disorder. It is well known that depression arises from a complex interaction between biological, social, psychological, and, of course, epigenetic factors. People facing adverse life events are, indeed, more likely to develop a mental disorder, especially depression, so it is not surprising that the incidence of depression has risen dramatically in the past year, with predictions for this year and the next being even worse. The current socio-health situation not only exacerbates mental health problems and impoverishes the population, but it also makes it difficult to access effective treatments or

undertake preventive measures. This fact, along with the interrelationship between depression and physical health, has led to a worrying decrease in public health worldwide; therefore, depression is one of the priorities WHO's Mental Health Gap Action Programme. Because depression is a multifactorial disorder, its development can depend on different effects that can cause dysfunctions in neural networks and neurotransmission systems. For example, some depressed patients have been shown to suffer a decrease in monoamines and their metabolites, as well as the corresponding transporters and precursors. These findings led to the formulation of the monoaminergic hypothesis of depression, which is the basis for the standard pharmacological treatment of the disease. To date, however, it has not been possible to demonstrate this hypothesis conclusively; although treated patients generally regain their normal mood and behavior, it cannot be said that antidepressants “normalize” brain activity because the brains of patients treated with antidepressants are in a different state than those of people who are not depressed. In addition, various studies have also reported on the existence of a dysfunction of the HPA axis underlying depressive disorders, as well as the role of corticosteroids through the release of the corresponding hormones, such as the CRH in the paraventricular nucleus of the hypothalamus, the ACTH in the pituitary gland, and cortisol in the adrenal glands. In depressed patients, circulating cortisol is increased, while alterations in the function of glucocorticoid receptors or the deterioration of negative feedback in the HPA axis play a central role in resistance to these hormones. In this sense, various researchers have argued that psychoneuroimmunological dysfunction underlies major depressive disorders, as documented by several studies, which found that depressed patients present alterations in both the peripheral immune system and cellular immunity, as well as elevated levels of proinflammatory mediators [8]. Multiple theories have questioned the monoaminergic hypothesis and tried to explain the biological changes that occur in depression; some of these will be discussed briefly here since they were examined more extensively in a previous review of preclinical studies on the use of medicinal plants in depression. Physiological or psychological conditions that activate the immune system also seem to make patients more susceptible to depression. Therefore, among the explanations regarding the pathophysiology of depression, the relationship between depression and inflammation

has emerged as playing a relevant role. Currently, there are at least ten different families of antidepressants used for pharmacological treatment, with their differences not due to their efficacy, but rather to their tolerability profile. Moreover, inflammation probably plays a large role in the response to antidepressant treatment. The presence of high levels of proinflammatory mediators in patients with depression has allowed researchers to establish a clear relationship between depression and inflammation. The symptoms of cytokine-induced depression in patients undergoing immunotherapy do not differ from a major depressive disorder of unknown etiology, and antidepressants may be effective for both.

It has been shown that antidepressants decrease the inflammatory response and proinflammatory factors, such as IL-2, IL-6, TNF- α , and interferon- γ , and that the levels of these mediators are higher more frequently in individuals who do not respond to antidepressant treatment. Moreover, cyclooxygenase-2 inhibitors and TNF antagonists may increase the effects of antidepressant treatments in some people, suggesting the possibility of a subtype of inflammatory depression. All these findings indicate that cytokines seem to contribute to depression, both through their involvement in brain neurotransmission as well as their role in neuroendocrine functions. Importantly, changes in brain volume and a reduction in gray matter density have been observed in several areas of the brain in depressed people, namely, the hippocampus, anterior cingulum, left amygdala, and right dorsomedial prefrontal cortex, all of which led to significant alterations in the homeostasis of neural circuitry. In contrast, therapies that focus on provoking plasticity enhancements by promoting BDNF secretion in the brain, e.g., neurogenesis, dendritic branching, and synaptogenesis, have been shown to have antidepressant effects, with an increase in serum being associated with recovery. These facts reinforce other possible hypotheses, such as the neuroplasticity or neurotrophic hypotheses, as possible explanations for the pathophysiology of depression. Oxidative and nitrosative damage also cause neurodegeneration, apoptosis, and reduction of neurogenesis and neuronal plasticity, leading to mitochondrial alterations, mitochondrial DNA damage, and a reduction of ATP production. In the case of the relationship between depression and oxidative stress, some drugs can reduce the increase in markers of oxidative stress while

producing a regulated increase in Nrf2, which is involved in the expression of different genes and antioxidant enzymes. In this context, compounds with antioxidant properties could be of interest in the treatment of depression. These include melatonin, which has also demonstrated its ability to reestablish and adjust circadian rhythms, disruptions of which frequently accompany mood disorders. Another example is the phenolic curcumin, which has been shown to regulate NO levels, possibly through the inhibition of iNOS, as well as the activity of Nnos in humans. Since NO is elevated in patients with major depression, a decrease in these levels could induce antidepressant effects, especially through the modulation exerted by NO on the production of neurotransmitters such as NA, 5-HT, and DA. Consistent with these results, studies have found that the administration of cytokines induces behavioral changes through MAOs, modifying their uptake from the synaptic cleft into presynaptic neurons or modifying the transport, such as serotonin transporter (SERT), selective serotonin uptake inhibitor (SSRI) or selective serotonin reuptake enhancer (SSRE). Another hypothesis for the pathogenesis of depression is the glutamatergic assumption, which postulates that glutamate signaling in the brain may be responsible for impairing neuroplasticity and that it may actually lead to neuronal death by excitotoxicity processes, if excessive. This theory is supported by the extraordinary clinical antidepressant effects that i.v. infusion of ketamine, an NMDA antagonist, produces in treatment-resistant patients, although this effect is short-lasting. It seems logical that if glutamate plays a role, then the inhibition or neurotransmitter GABA is also involved, both through its action on the neuroendocrine system, and also by exerting neuroprotective effects. Many medicinal plants have been described as potential antidepressant agents and a relevant group of them has been tested in animal models with different results. In a previous review [9], we compiled papers published between the years 2000 and 2020 in which these plants were cited as antidepressant-like agents and studied in vivo (using animals) or in vitro for their effects on various biochemical and physiological systems. Some of them have been shown to inhibit the expression of cytokines, while others seem to act directly on monoamines, modifying their expression, metabolism, reuptake, or effect on the target. Others exhibit antioxidant effects that can reduce neuronal alterations and damage. The aim of

this review is, thus, to present and discuss the available evidence for the use of medicinal plants as antidepressant agents in clinical trials. Although treatments for depression can be derived from traditional practice and natural plants, the aim should be to establish their efficacy and safety through rigorous clinical trials. This narrative review examines the principal species tested and their possible mechanisms of action against depression as shown in clinical studies, as well as their general potential. It also presents the possibility of using some of them as adjuvants in the treatment of this disease. We have thus compiled all articles written in English since the year 2000 that were cited in the Cochrane Central Register of Controlled Trials, PubMed, and the Web of Science databases. The key words employed for this review were “antidepressant”, “medicinal plants”, “natural products”, and “clinical trials”. Our principal focus was on clinical trials that assayed the efficacy of the plants cited as antidepressants in the literature; of these, we selected those plants that had previously been studied in animal experiments with positive results. From the 183 species selected, to the best of our knowledge, only 17 have been subjected to some sort of clinical trial, with 6 offering relevant results and 3 (saffron, turmeric, and St. John’s wort) having an extensive and complete description of properties. In this review, different rating scales for depression are cited. Some are used extensively while others are more specific and were employed only in a limited group of trials

ROLE OF DEPRESSION :

Biological differences. People with depression appear to have physical changes in their brains. The significance of these changes is still uncertain, but may eventually help pinpoint causes.

Brain chemistry. Neurotransmitters are naturally occurring brain chemicals that likely play a role in depression. Recent research indicates that changes in the function and effect of these neurotransmitters and how they interact with neurocircuits involved in maintaining mood stability may play a significant role in depression and its treatment.

Hormones. Changes in the body's balance

of hormones may be involved in causing or triggering depression. Hormone changes can result with pregnancy and during the weeks or months after delivery (postpartum) and from thyroid problems, menopause or a number of other conditions.

Inherited traits. Depression is more common in people whose blood relatives also have this condition. Researchers are trying to find genes that may be involved in causing depression.

METABOLIC PATHWAY OF KYNEURINIC ACID IN SCHIZOPRENIA :

Although the pathophysiology of schizophrenia is currently unclear, inflammation has been suggested to play an important role in the pathophysiology (1, 2). In addition, there is growing evidence of an interaction between inflammation and the kynurenine (Kyn) pathway in schizophrenia (3). The Kyn pathway is regulated by the immune system, and the decomposition of tryptophan via the Kyn pathway is activated by proinflammatory cytokines. The Kyn pathway is also considered to crosstalk with the immune system, proinflammatory cytokines, and neurotrophic factors. Tryptophan (Trp) is degraded to Kyn, which is catabolized to either kynurenic acid (KynA) via kynurenine aminotransferases or to 3-hydroxykynurenine (3-HK) via kynurenine 3-monooxygenase and finally to quinolinic acid (QA). Proinflammatory cytokines, including interleukin-1 β (IL-1 β), IL-6, and tumor necrosis factor- α (TNF- α), are thought to contribute to the pathogenesis of psychiatric symptoms in schizophrenia by Kyn pathway activation. Kyn metabolites affect neurotransmission and cause neurotoxicity. Several studies have indicated that proinflammatory cytokines and the Kyn pathway in the blood are dysregulated in patients with schizophrenia. Increase in the plasma levels of proinflammatory cytokines, such as IL-1 β , IL-6, and TNF- α , have been consistently reported in patients with schizophrenia. C-reactive protein (CRP) levels have also been reported to be elevated in patients with schizophrenia. Thus, these proinflammatory cytokines may accelerate the Kyn pathway, which may be related to changes in neurotrophic factors, which are associated with the symptoms of schizophrenia.

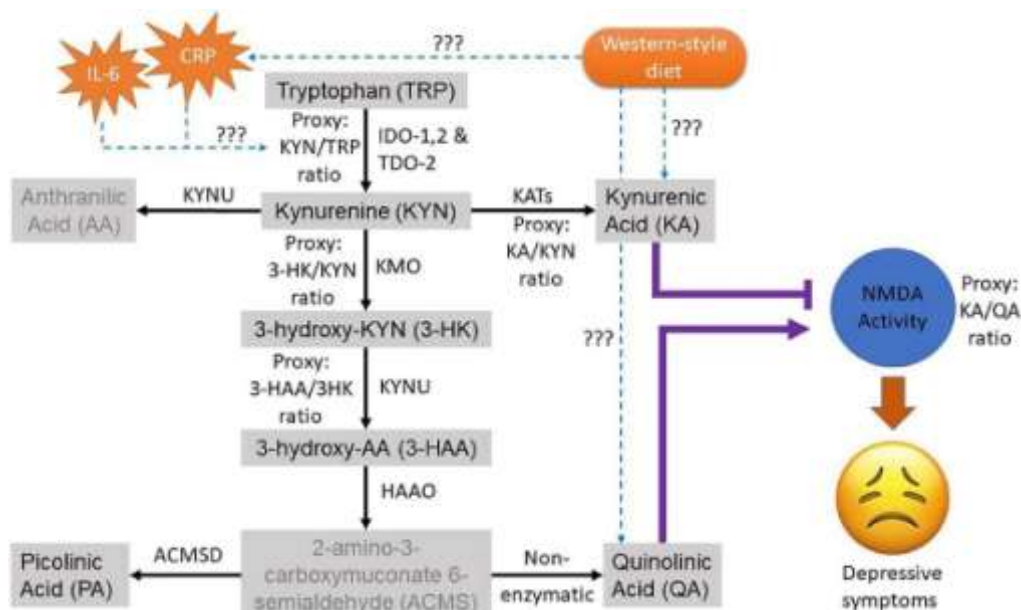


FIG.1.KYNEURINIC ACID AND QUINOLINIC ACID PATHWAY IN DEPRESSION

Here, kynurenic acid acts as a NMDA antagonist and relieves the depression, while quinolinic acid is a NMDA agonist, which causes depression.

So, Depression is as a result of imbalance of kynurenic acid and quinolinic acid.

On this studies reveals that increasing the level of kynurenic acid constitute the relief from depression..which further improve schizophrenia treatment.

Finally our research findings reveals that ,camellia sinensis-pur-eh extract constitute kynurenicacid,which is found to be a constituent by LC-MS, Quantification studies.

CAMELLIA SINENSIS :

The plant *Camellia sinensis* is the source of different teas (white, green, yellow, oolong, black, and pu-eh) consumed worldwide, which are classified by the oxidation degree of their bioactive compounds. The sensory (taste, aroma, and body of the drink) and functional properties of teas are affected by the amount of methylxanthines (caffeine and theobromine), amino acids (L-theanine) and reducing sugars in their composition. Additionally, flavan-3-ols, mainly characterized by epicatechins, catechins, and their derivatives, represent on average, 60% of the bioactive compounds in teas. These secondary metabolites from teas are widely recognized for their antioxidant, anti-cancer, and anti-inflammatory

properties. Thus, *Camellia sinensis* extracts and their isolated compounds have been increasingly used by the food industry. However, bioactive compounds are very susceptible to the oxidation caused by processing and degradation under physiological conditions of gastrointestinal digestion. In this context, new approaches/technologies have been developed for the preservation of these compounds. This review presents the main stages involved in production of *Camellia sinensis* teas following a description of their main bioactive compounds, biological properties, stability and bioaccessibility. Besides, and updated view of *Camellia sinensis* teas in the field of food science and technology was provided by focusing on novel findings and innovations published in scientific literature over the last five years.

Camellia sinensis flowers and leaves have a rich composition of bioactive compounds such as phenolic compounds (phenolic acids, flavonoids and tannins), alkaloids (methylxanthines) and nutrients (carbohydrates, proteins and minerals) (Sharma, Verma, & Kumar, 2021). The chemical composition of the flower, from which white tea originates, consists of 34% carbohydrates (glucose, fructose, sucrose, and polysaccharides), 12% phenolic compounds (PCs), 28% crude proteins and 3% saponins

TYPES OF TEA EXTRACT



FIG.2.TYPES OF EXTRACT

PREPARATION OF TEA EXTRACT – TEA PUE-RH:

Tea leaves are collected locally from Munnar and used for the extract which is authenticated with reference (17P\1\211\2023\13109)

BOTANICAL PROFILE:

KINGDOM : Plantae CLADE :
 Tracheophytes CLADE : Angiosperms
 CLADE : Eudicots

ORDER : Ericales FAMILY :
 Theaceae GENUS : Camellia
 SPECIES : C.sinensis

Camellia sinensis is a species of evergreen shrub or small tree in the flowering plant family Theaceae. Its leaves, leaf buds, and stems can be used to produce tea. Common names include tea plant, tea shrub, and tea tree (unrelated to *Melaleuca alternifolia*, the source of tea tree oil, or the genus *Leptospermum* commonly called tea tree).

White tea, yellow tea, green tea, oolong, dark tea (which includes pu-erh tea) and black tea are all harvested from one of

two major varieties grown today, *C.sinensis* var. *sinensis* and *C.s.* var. *asamica*, but are processed differently to attain varying levels of oxidation with black tea being the most oxidized and green being the least. *Kukicha* (twig tea) is also harvested from *C. sinensis*, but uses twigs and stems rather than leaves.

Teas are commonly prepared by an infusion technique, which consists of adding the plant matrix in a container with boiling water (up to 100 °C), capping, and letting it rest from 5 to 10 production of tea herbs involves up to five-unit operations, known as withering, panning or steaming, sweltering, rolling, and drying. The more steps, the higher the reduction in the concentration of bioactive compounds, mainly phenolic compounds. Furthermore, these operations alter the concentration of methylxanthines, theaflavins, amino acids and volatile compounds, and consequently their bioactive properties, resulting in different types of teas based on different processing stages, has different concentrations of phenolic compounds. The withering step aims to reduce the moisture in the tea leaves, making them soft and leathery and to modify sensory characteristics of teas such as taste and aroma.

During this step, the phenolic profile is

modified, especially in flavan-3-ols, predominantly epicatechins (90%), which represent between 60 and 70% of the total phenolic compounds. .

It found 172 different volatile compounds, which were formed and/or modified during the withering step in white tea. Withering reduces the concentration of reducing sugars and increases the concentration of caffeine in tea, as well as oxidase enzymes. The polyphenol oxidase (PPO) and peroxidase (POD) enzymes play an important role in tea processing since catalyze the oxidation reactions of phenolic compounds.

Yilmaz, Ozdemir, " and Gokmen " (2020) demonstrated that the total free amino acid content of teas increased in the withering stage while decreasing in the drying stage, proving that different stages of tea processing affect the level of GABA (Gamma- aminobutyric acid), kynurenic acid, and dopamine. According to these authors, GABA and kynurenic acid concentration of tea increased 33% and 53% after withering, respectively. In comparison, the tea that went through the drying process showed lower GABA and kynurenic acid than withered tea. Among the studied teas, white tea presents a higher concentration of phenolic compounds, due to the simpler processing, which involves only the withering steps, followed by drying . In this way, the process of obtaining white tea dispenses with any steps of enzymatic inactivation and fermentation, providing an unequalled flavor.

Their flavor is described as slightly sweet/umami and fresh/green odor . Therefore, white tea is considered an unfermented tea with a low degree of oxidation of phenolic compounds . The steaming step, also known as panning or roasting, is carried out in order to inhibit enzymes responsible for the enzymatic browning process. In the presence of oxygen, the enzyme group of polyphenol oxidase (PPO), catalyzes the hydroxylation of monophenols, forming o-diphenols, followed by the oxidation of odiphenols, resulting in o-quinones and dark pigments called melanoidins . As these enzymes are thermosensitive, the steam treatment is effective in enzymatic denaturation . However, phenolic compounds are also susceptible to degradation at high temperatures. Thus, the time and temperature used in the process must be strictly controlled during the process. High pressure assisted freezing and high-intensity ultrasound may be alternatives for the denaturation of PPO, reducing damage to the concentration of polyphenols.

WHITE TEA EXTRACT CONTAINS LARGE AMOUNT OF KYNEURINIC ACID, WHICH IS ALSO CALLED AS PUE- RH TEA
KYNEURINIC ACID ISOLATION IN TEA BY LC-MS:

The kynurenic (KYN) pathway is implicated in diseases such as cancer, psychiatric, neurodegenerative and autoimmune disorders. Measurement of KYN metabolite levels will help elucidating the involvement of the KYN pathway in the disease pathology and inform drug development.

Methodology: Samples of WHITE TEA EXTRACT spiked with deuterated internal standards, processed and analyzed by LC- MS/MS; analytes were chromatographically separated by gradient elution on a C18 reversed phase analytical column without derivatization.

Preparation of standard & IS stock solutions Stock solutions were prepared individually for each standard and IS in a final concentration of 1 mmol/l. According to their solubility and stability in solution, several solvents and mixtures were used: TRP, d5-TRP, 3-HAA, PICO, QUIN, d3-QUIN, 5-HT and d4-5-HT were dissolved in water/methanol/FA/ 10.4155/bio-2016-0111. Ascorbic acid (50/50/0.1/0.02). KYN, d4-KYN, 3-HK and MEL were dissolved in MeOH with 0.1% formic and 0.02% ascorbic acid. DA and d4-DA were dissolved in water with 0.1% formic and 0.02% ascorbic acid. KYNA, d5-KYNA, XANA and NEO were dissolved in dimethyl sulfoxide. All standard stocks were prepared on ice; aliquots were aerated with nitrogen and stored at - 80°C until use. Preparation of working dilutions for calibration & IS Stock solutions were diluted with acidified mobile phase (0.2% FA/0.05% TFA/1% ACN in water; components similar to mobile phase A, higher concentration of organic acids) to generate standard dilution mixtures of all standards in a range of 0.1–10,000 nmol/l for analysis of brain tissue and CSF and 1–100,000 nmol/l for analysis of plasma. Calibration standards were prepared with concentrations of 1×10^x , 2.5×10^x , 5×10^x , 7.5×10^x mol/l ($x = -10, -9, -8, -7, -6, -5, -4$). An internal standard mix (IS-MIX) was prepared in acidified mobile phase with the following concentrations: d5-TRP 10 μ mol/l, d4-KYN 1 μ mol/l, d4-5-HT 1 μ mol/l, d4-DA 1 μ mol/l, d3-QUIN 1 μ mol/l, d5-KYNA 0.1 μ mol/l. These concentrations were chosen based on endogenous levels of analytes and an adequate S/N to ensure reliable peaks. Preparation of calibration standards, samples & quality control samples

Plasma To 10 µl of sample or 10 µl of calibration standard, 10 µl of IS- MIX and 10 µl of acidified mobile phase were added (quality control samples [QCs] were prepared according to the method of standard addition: QCs consisted of 10 µl pooled plasma from study samples + 10 µl IS-MIX and 10 µl calibration standard without addition of acidified mobile phase). Subsequently 150 µl ice-cold MeOH was added and this mixture was allowed to rest for 30 min at -20°C to support protein precipitation. After centrifugation (3000 × g, 4°C, 15 min) supernatants were removed and evaporated to dryness under a gentle stream of nitrogen. Dried extracts were reconstituted in 50 µl of acidified mobile phase. Twenty microliters were injected into the LC–MS/MS system. No additional filtration step was necessary. All steps including the evaporation were carried out in 96-well plates to provide sufficient sample throughput.. The dried extract was reconstituted in 40 µl of acidified mobile phase. A total of 20 µl were injected into the LC– MS/MS system. No additional filtration step was necessary. All steps, including the evaporation, were carried out in 96-well plates to

allow for sufficient sample throughput screening.

IV. RESULTS &DISCUSSION :

Each analyte was first infused into the mass spectrometer and turned for its molecular transitions.

Positive ESI mode turned out to be superior for all molecules even for those with carboxylic functional groups without primary amine function (QUIN,PICO,KYNA and XANA).

Since ion source parameters are dependent on flow rate and mobile phase composition, these parameters were optimized via flow injection analysis after HPL method development was done and final mobile phase conditions,gradient etc., were established. 4.tR value for kynurinic acid was found to be 2.04 with accuracy range of 95 – 100 , when compared with precision ranges of 24 – 73 and LCOQ was found to be 0.25. 5.The concentration of kynurinic acid was found to be 47 ± 18 nmol/l.

TABLE 1 :

Table 1. Mass transitions, declustering potential and collision energy.				
Analyte	Q1 mass (m/z)	Q3 mass (m/z)	DP (V)	CE (V)
Tryptophan	205.1	118.0	39.0	28.0
Kynurenine	209.1	94.1	41.0	19.6
3-OH-kynurenine	225.1	110.0	41.4	22.9
3-OH-anthranilic acid	154.0	136.0	40.0	17.0
Quinolinic acid	168.0	124.0	33.0	19.7
Picolinic acid	124.0	78.0	36.0	29.0
Kynurenic acid	190.1	162.0	65.0	24.0
Xanthurenic acid	206.0	178.0	66.0	25.5
Serotonin	177.1	160.0	37.0	15.0
Dopamine	154.1	137.0	42.0	15.0
Neopterin	254.1	206.1	85.5	26.2
Melatonin	233.1	174.0	50.0	21.5
IDO inhibitor	438.1	359.0	75.0	22.0
d5-Tryptophan	210.1	122.1	38.0	39.8
d4-Kynurenine	213.1	140.1	39.0	21.0
d3-Quinolinic acid	171.0	127.0	37.0	20.0
d5-Kynurenic acid	195.1	167.1	65.0	24.0
d4-Serotonin	181.1	164.0	36.0	18.0
d4-Dopamine	158.1	141.1	42.0	15.5

TABLE :2

Table 2. Retention times, assigned internal standard, LLOQ and accuracy and precision.

Analyte	t_r (min)	IS	Accuracy (%)		Precision (%)		LLOQ (nM)
			Within-run	Between-run	Within-run	Between-run	
Tryptophan	1.98	d5-TRP	100-111	97-108	1.2-5.9	2.5-5.4	2.5
Kynurenine	1.74	d4-KYN	99-102	100-106	2.1-5.8	3.4-8.5	0.5
3-OH-kynurenine	1.31	d4-KYN	81-100	90-94	2.4-6.8	3.9-10.3	0.75
3-OH-anthranilic acid	1.79	d4-KYN	42-67	59-74	13-23	14-20	1.0
Quinolinic acid	0.97	d3-QUIN	98-105	100-101	1.5-6.5	3.8-8.1	2.5
Picolinic acid	1.02	d3-QUIN	97-105	101-116	3.6-6.6	4.7-14.3	10
Kynurenic acid	2.04	d5-KYNA	95-100	99-109	2.4-4.5	3.4-7.3	0.25
Xanthurenic acid	1.98	d5-TRP	89-100	95-111	3.8-9.6	6.2-11.5	0.25
Serotonin	1.78	d4-5-HT	99-102	100-101	1.0-6.9	2.5-3.3	0.25
Dopamine	1.07	d4-DA	96-103	98-100	1.2-10.7	4.4-6.5	0.5
Neopterin	0.95	d3-QUIN	109-113	111-114	5.1-5.6	5.4-9.3	1.0
Melatonin	2.46	D5-KYNA	Out of acceptable range		Out of acceptable range		
IDO-inhibitor	2.75		Represents an example for individualization of the method				

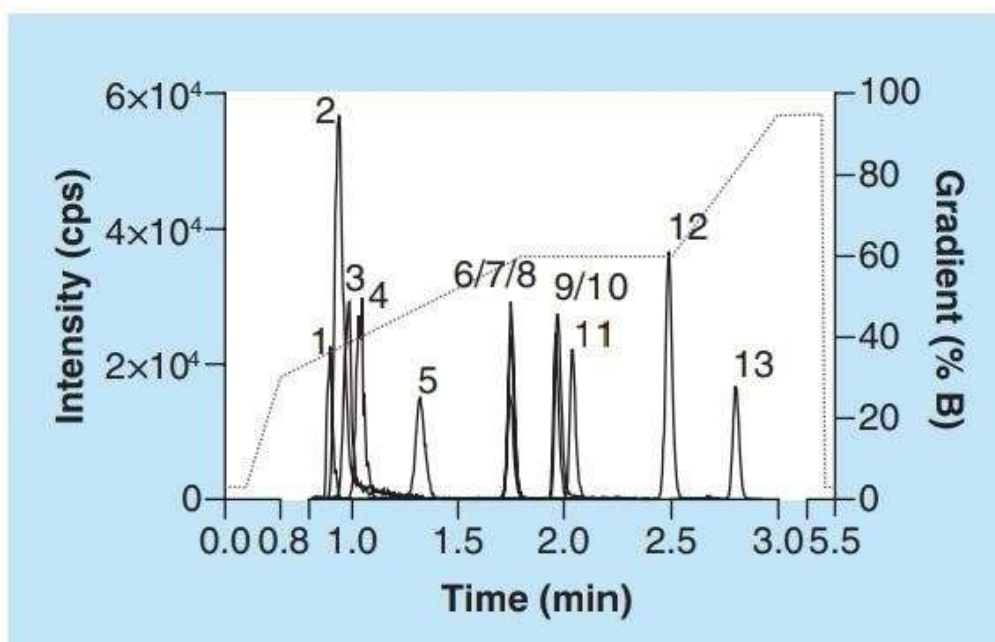


FIG.1. Representative chromatogram of a standard sample (1 neopterin [1000 nM], 2 quinolinic acid [250 nM] + d5-quinolinic acid, 3 picolinic acid [1000 nM], 4 dopamine [500nM] + d4-dopamine, 5 3-hydroxykynurenine [1000 nM], 6kynurenine [1000 nM] + d4-kynurenine, 7 serotonin [250 nM] + d4-serotonin, 8 3-hydroxyanthranilic acid [1000 nM], 9 tryptophan [1000 nM] + d5-tryptophan, 10 xanthurenic acid [250 nM], 11 kynurenic acid [250 nM] + d5-kynurenic acid, 12 melatonin [25 nM], 13 IDO1 inhibitor [500 nM], dotted line represents the theoretical gradient profile).

V. CONCLUSIONS

1.A sensitive and reliable method have been established which allows a reasonable,efficient analysis.

2.The presence of kyneurinic acid in camellia sinensis,have proven futuristic hope in schizophrenia.

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