



Proposed Vaccine for Mental Health: From Green Tea

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ABSTRACT

Mental health is one of the major concerns prevailing now-a-days, both, at national level and global level. Specially, after COVID-19, this concern has raised to an alarming level, and needs to be worked upon. Although, there are various therapies and medications against mental disorders. But, those medicines have their own side effects also. We need to take some extra step towards the root of these mental disorders, which is 'psychological stress'. Psychological stress is not only the root of various mental disorders, but also, a few physical health issues, such as type-2 diabetes mellitus, cardiovascular diseases, cancer, etc. That's why; we do need therapeutic agents and their target against psychological stress. A few publications on PubMed claimed that, green tea has a few such natural components. Two phytochemicals of green tea 'caffeine' and 'L-theanine', acts on brain, and can positively influence mood and cognition. Both these components in this research were studied using 'PubChem' and 'ADMETlab2.0'. Caffeine mainly enhances arousal, alertness, and, attention-switching. While, L-theanine can increase the level of happiness promoting neurotransmitters in brain, which are serotonin, dopamine and GABA, as suggested by 'PubChem'. ADMETlab2.0 suggests the overall safety of both these phytochemicals on human body. So, the final conclusion of this research was that, mainly 'L-theanine' as key component or 'L-theanine' and 'caffeine' together, isolated from green tea, can serve as 'preventive or therapeutic vaccine' against various mental disorders and psychological stress.

Keywords: Mental health, Mental disorders, Psychological stress, Green tea, Phytochemicals, Caffeine, L-theanine, Serotonin, Dopamine, GABA, PubChem, ADMETlab2.0, Preventive or therapeutic vaccine

INTRODUCTION

Mental health

Research attention and interventions are not so well established for improving the mental health in young people. Although, some attention has been received towards enhancing the mental health in young people, for both those who have the mental disorders, as well as, those who don't have any of the mental disorders. It is quite difficult to define a good mental health. European College of Neuropsychopharmacology Thematic Working group on the prevention of mental disorders and mental health promotion (ECNP TWG PMD-MHP), has presented a critical review of the available operationalizations for good mental health, which is a necessary step for achieving a more standardized research on mental health. A good mental health represents that state of well-being, which help us cope

well with normal difficulties of life and still work well with good productivity. Some of the domains which define a good mental health involves [1].

- Knowledge about mental health.
- Our attitude towards mental disorders.
- Our perception about ourselves and our values.
- Cognition related skills.
- Performance in academics and occupation.
- Our emotions.
- Our behaviour.
- Our strategies for self-management.
- Our social skills.
- Our relationships with our family members and other people.
- Our physical health.
- Sexual health.
- Meaning of life.
- Quality of our life.

These domains maybe useful for doing research in field of good mental health and can also be of great help for improving the mental health.

Both, our physical health and mental health are strongly connected to each other. But those pathways are still not very clear, by which one of them effects the other. Although we study the effect of past mental health on present physical health and past physical health on present mental health. This effect maybe caused directly or indirectly, from our past health status. The measurement of mental health is done using-Centre for Epidemiological Studies Depression Scale (CES), whereas, for measuring the physical health we analyse-Activities of Daily Living (ADL). Both direct and indirect effects of both forms of health have been studied. Indirect effects shows that past mental health cause 10% effect on the physical health, and, past physical health cause 8% effect on the mental health. Physical activity has the greatest role in these indirect effects. Stronger indirect effects have been observed in males and in people of old age groups also. Health policies, which have the goal of bringing about some change in physical and mental health, needs to consider, not only the direct cross effects of both types health, but, also the indirect cross-effects between them [2].

12 epidemiological studies were performed to check whether there's some link between the diet and mental health or not-in children and adolescents. Out of 12, 9 candidates were checked with diet as exposure, while, the remaining 3 candidates were checked with mental health as exposure. In this study, some of the evidences were found which showed a cross-sectional relationship between unhealthy eating habits and poor mental health in children and adolescents. Some observations also showed the relationship between the good quality diet and better mental health.

A few literatures were surveyed on 'PubMed', to get a basic idea about mental health and some of the facts associated with it. After surveying the above-mentioned 3 literatures, got an idea about the definition of good mental health, and, some of the parameters, whose well-being represents a good mental health. We can also see that, mental health and physical health are directly or indirectly connected to each other. Thus, both of them demands our attention and research for improvement in their current status. Also, our diet's quality effects our mental health. From the above-mentioned literature surveys, we can conclude that-mental health demands, more and more research, not only for its self-improvement but also for improvement of physical health. This research had the aim to slightly fulfill this demand.

But, before that, let us study and analyse the status of mental health in India and also at the global level, to get a deep understanding about the level of attention it demands.

Mental health India

In the literature survey, a comprehensive approach was applied, and, relevant studies were analysed, which provided information about mental health problems in India. In this study, many databases were used for literature survey, such as-PubMed, PsycINFO and Google scholar. In the literature survey, a combination of these keywords were used "mental health", "India", "prevalence", "burden", "access to care" and "mental health disorders". In the literature

survey there were no restrictions, associated with date or language and a wide range of studies were done. Information related to this topic were collected from multiple different sources, which involved-academic literature, reports from government agencies, international organizations and non-government organizations. All these were studied to get a holistic understanding about this topic. In this study, both qualitative and quantitative studies were considered. The literature survey provided the information on many aspects associated with mental health and its status in India.

In India, there are many patients of mental health disorders in its population. Epidemiological studies reports that 9.5 to 370 per 1000 individuals in India are suffering from various psychiatric disorders. Some of the common mental health disorders in India are-depression, anxiety disorders, bipolar disorders, schizophrenia and substance use disorders. Depression is mainly shown by-persistent sadness, hopelessness and no interest in any of the activities. 3.5% deaths in the population occurs due to anxiety or depression. This disease effects-patient's mood, thoughts, behavior and his/her physical health also. The symptoms of this disease are-fatigue, changes in appetite, changes in sleep, loss of concentration and focus and, self-harm and suicidal thoughts. This disease can change-a person's everyday life, different relationships of the patient and quality of his/her life. Anxiety disorders are mainly shown by excessive and persistent worry, fear, or anxiety, which interferes with the patient's daily life. There are various types of anxiety disorders. In generalized anxiety disorder, patients have chronic and excessive worry about various aspects of life in their heart. In panic disorders, recurrent panic attack occurs, also overwhelming fear shows up along with a few physical symptoms, such as heart palpitations and shortness of breath. Phobias are characterized by, intense fear of specific objects, situations or activities. Obsessive-Compulsive Disorder (OCD) has intrusive thoughts (obsessions) and repetitive behaviours (compulsions), which are done reduce anxiety. Anxiety disorders can lead to-distress, avoidance behaviour and impaired functioning. In Bipolar disorder, both Mania (elevated mood) and Depression are alternately and periodically shown by the patients. During the period of Mania patients have high energy, less sleep, racing thoughts, increased self-esteem, impulsive behaviour and high sense of self-importance. On the other hand, during the period of depression sadness, loss of interest, fatigue, and changes in appetite and sleep, shows up. This disorder can effect patient's emotions, behaviour, relationships and overall functioning. Schizophrenia is a chronic mental disorder in which, patient's perception of reality, thinking, emotions and behaviour gets changed. Common symptoms of this disease are hallucinations (perceptions in absence of any stimulus, that has the qualities of real perceptions), delusions (false beliefs), disorganized speech and behaviour, less expression of emotions, and, social withdrawal. The patients of schizophrenia may also face difficulties associated with-memory, attention and executive functioning. Ability to think, interact with others, and function in society may also get impaired. Substance use disorders are shown by-using various harmful substances in excess amount and compulsive way. Those harmful substances are-alcohol, drugs, etc. Patients take them, despite their negative consequences. Usage of these substances may cause-addiction of their consumption, dependence on them and withdrawal symptoms when these are not given to the person. These substances may affect the mental health also and may lead to-mood disorders, anxiety disorders, psychosis, etc.

In India, there are many social and cultural factors, which may influence a person's mental health. Those factors are-social stigma and discrimination, lack of gender equality, poverty and socioeconomic problems, rapid urbanization and migration, family dynamics and pressure of society, cultural beliefs associated with mental illness, shortage of mental healthcare professionals, lack of enough resources and infrastructures, lack of awareness and stigma, etc. Like, in India, many women since olden days have faced so many hardships and difficulties. This can lead to the development of stress, anxiety or depression in them. As a result, they are more likely to experience mental health problems than men. Similarly, other factors, such as, shifting from village to town or city or migration between cities are also likely to cause mental health problems in people, due to-lack of social support, higher level of stress, etc. But, India is taking so many initiatives towards mental health also, such as-government programs and policies for mental health, community-based mental health services, integration of mental health into primary healthcare, awareness campaigns and advocacy efforts.

From literature survey, it is quite clear that, India is becoming aware about mental health with time and taking steps towards improvement of its status. But, mental health status in India, demands more and more attention and scientific approaches for its improvement. This research was one such scientific approach [3].

LITERATURE REVIEW

Mental health-globe

At the global level, mental and substance use disorders are some of the main causes of disabilities. More than 970 million cases of depression and anxiety disorders have been reported globally in 2019. Substance use disorders have also increased since 1990. There are more than 108 million patients of alcohol use disorders and more than 56 million patients of drug use disorders across the globe. Disorders based on usage of Opioid accounts for 22% of the drug use disorders [4].

As per recent estimates, at the global level, 13% of adolescents have mental disorders. Most commonly seen mental disorders are-anxiety and depression. These disorders account for 40% of all mental disorders. Different genders also show different types of more commonly observed mental disorders in them. Like, in females depression and anxiety are more common, whereas, in males Attention Deficit Hyperactivity Disorder (ADHD) and conduct disorder are more common. Substance use disorders are also more common in males than females. Males with this disorder are approximately two times more in number than females.

Global pandemic of COVID-19 also had a great influence on mental health. A recent GBD paper reported that, there were an additional 53.2 million cases of depression and 76.2 million cases of anxiety, which showed up and enhanced because of COVID-19 pandemic. This pandemic also increased the risk of suicides [5].

Some treatment approaches, such as, 'integrated care' and 'task shifting' have been shown to be promising against mental disorders, but, there are many challenges in implementing them. There has been progress in the field of Global Mental Health (GMH) also, but still, some efforts are underway. GMH and researches are likely to evolve with time.

It is clear that, mental health demands a great amount of attention, at the global level also, and, more and more scientific approaches against mental disorders. Now, let us take a look at, some of the common mental disorders and some medications and therapies available against those disorders [6].

Current treatment-mental disorders

Depression: It is a mood disorder, which makes the patient feel sad and hopeless. These feelings retain for a longer duration. The patient may lose interest in those activities which they used to enjoy earlier. These feelings sadness and hopelessness interferes with day to day life. There are a few chemicals in the brain, which effects our mood. Changes at the level of those chemicals cause depression. Serotonin is the main neurotransmitter, studied in case of depression. There's a reduction in this neurotransmitter, within the patient's brain, when the symptoms of depression, shows up. This fact has been confirmed from tryptophan-deletion based study [7].

There are various reasons, which may cause depression-stressful events, such as death of a loved one, divorce or unemployment; family history of depression; any chronic disease, such as, diabetes, heart disease or cancer; consumption of drugs or alcohol. These reasons may increase the risk of depression.

Treatment of depression depends upon the severity of the patient's symptoms. The patient may be treated using either Cognitive Behavioural Therapy (CBT) or antidepressant medicines. CBT teaches the patient to identify and deal with the negative thoughts. Antidepressant medicines are those chemical substances which are given the patient to reduce or manage his/her symptoms. These medicines may be provided for several weeks, before they start working. Some of the anti-depressant medicines, which can have given to the patients of depression are:

- Bupropion (Generic name-Bupropion) it is an antidepressant drug, which can be used to treat depression and seasonal affective disorder. It can also be used for smoking cessation and weight management. This drug can help improve-mood regulation, nicotine craving and when it gets combined with naltrexone, helps reduce food intake also. It is thought, that this medicine works, by changing the levels of a few chemicals in the patient's brain, which includes noradrenaline and dopamine also. It was approved by- 'food and drug administration' on 30th. December. 1985. Common side effects of this drug may include-dry mouth, ringing in the ears, blurred vision, nausea, vomiting, loss of appetite, sleep problems, etc.
- Zoloft-(Generic name-Sertraline) it is an antidepressant drug, which is one of those medicines, which fall under the category of 'Selective Serotonin Reuptake Inhibitors (SSRI)'. It balances the level of serotonin in the brain

and the nerves. This drug not only has the potential to treat some types of depression, but, it can also be given to the patients of Premenstrual Dysphoric Disorder (PMDD), Social Anxiety Disorder (SAD), OCD, panic disorder and Post-Traumatic Stress Disorder (PTSD). Some of the side effects of this drug maybe a seizure, vision changes, unusual bleeding or bruising, etc.

- Sertraline-(Generic name-Sertraline) this also is that antidepressant drug, which falls under the category of SSRI. Along with depression, it also treats, OCD, SAD, PTSD and panic disorder.
- Cymbalta-(Generic name-Duloxetine) it is a Selective Serotonin and Norepinephrine Reuptake Inhibitor Antidepressant (SSNRI). It shows effect on those chemicals in the brain, which may not be balanced in the patients of depression. It can be utilized for the treatment of major depressive disorder in adults. This drug can also be used for the treatment of general anxiety disorder in children and adults who are at least 7 years old. It can also be used for the treatment of nerve pain which is seen in the patients of diabetes, or chronic muscle or joint pain also etc. are some of the currently available antidepressant medications against depression.
- As we can clearly see that the medications mentioned above, are not only effective against depression, but, against various other mental disorders also. These other mental disorders mostly include anxiety related problems and maybe some physical symptoms also. Also it is clearly visible that, many antidepressants targets 'serotonin', which has main role in causing depression. Thus, these diseases are curable, if with awareness, recognized on time.

Medicines and treatments are available against various other mental disorders also. Like 'schizophrenia', which is one of the serious mental disorders, can also be treated using medications.

Schizophrenia: It is a chronic mental disorder, which effects the patient's emotions, thinking and behaviour. Patient's brain faces difficulty in distinguishing between real and fake. Although, exact cause of Schizophrenia is not clearly known. But, lack of some chemical balances in the brain may cause this disease. Sometimes, some stressful events may also trigger and bring about some of the symptoms. These factors may also increase the risk of development of this disease-family history of schizophrenia; exposure of some of the substances such as, amphetamines and opiates [8].

Main symptoms of this disease are-delusion, hallucinations, disordered thinking and speech, extremely disorganized or abnormal movement, lack of drive or initiative. Delusions are a few false ideas, on which the patients strongly believe. Like, the patient may believe that, someone is constantly keeping an eye on him/her or monitoring his/her activities. Hallucination is to sense something from any of our sense organs, which is not real, but has the qualities real stimuli. The patient, while talking may also shift from one topic to another in a way, that doesn't make any sense. The patient may create his/her own words or sounds also. Other than these symptoms, the patient may do some movements which are not essential. The patient may also, not properly take care of his/her physical hygiene, may also avoid family and friends, become socially isolated, and, not function normally. Some of the therapies, which can be given to the patients of this disease are-assertive community treatment; cognitive behaviour therapy, which helps the patients to change some behaviours and handle delusions and hallucinations; illness management skills, in which the patient is taught to manage this disease; family psychoeducation, teaches family to be a part of patient's therapy; social skills training which helps the patient to become social and get rid of social isolation; supported employment is a form of therapy, in which the patients are placed into a job, as per their skills. This helps patients regain their independence and self-confidence.

Some of the medicines can also be used to cure this disease

- Seroquel (Generic name-Quetiapine) the patient of schizophrenia, should be at least 13 years old to use this medicine. This can not only treat schizophrenia, but, along with divalproex or lithium can also be used for the treatment of mania or also, depression of bipolar disorder. In combination with, other antidepressants, it can also be used for the treatment of major depressive disorder in adults. Some of the side effects of this medicine maybe high blood pressure, painful or difficult urination, etc.
- Abilify (Generic name-Aripiprazole) it is an antipsychotic medicine, which shows its effects by changing the actions of chemicals in brain. It can be used to treat various psychotic conditions in adults and teenagers. It can also be used in the treatment of other mental disorders, such as, bipolar I disorder, major depressive disorder in adults, Tourette's disorder in at least 6 years old children and symptoms of autistic disorder also. Some of the side effects of this medicine maybe-severe agitation, distress or restless feeling. Some uncontrollable movements of eyes, lips, tongue, etc.
- Latuda (Generic name-Lurasidone) It is also an antipsychotic medicine, which changes the effects of chemicals in the brain. It is given to teenagers and adults for the treatment of schizophrenia. It can also be used for the

treatment of depression episodes of bipolar disorder. Some of the side effects of this drug maybe-seizure, a light-headed feeling, trouble swallowing etc. are a few medicines against 'schizophrenia'.

Thus, we can conclude that, such a serious mental illness is also curable. "Now-a-days, medical science has achieved, so many breakthroughs that, we're shifting into the new light of hope that, we can recover from many illnesses and achieve a wonderful physical and mental well-being."

The medicines can be used, for the treatment of more than one mental disorders and problems, as it is clear from the above-mentioned contents. If I will describe in detail about, each and every medicine, then, I will probably write a book and this will not remain a research article. So, I stopped my exploration of currently available treatments of the mental disorders and I began to explore the facts about, the root of many mental disorders-the 'psychological stress'.

Psychological stress

Psychological stressors: These are some social and physical environmental circumstances, in which ability to adapt and resources of an organism are put into difficulty. Many different types of situations are involved in these circumstances [9].

Stressors influence all of these-our mood, sense of well-being, our behaviour and our health. In young, healthy people, response to acute stress may not cause any burden on health, as they may adapt to the acute stress responses. But in older or unhealthy people, in long-term, stressors may negatively impact their health also. There are many factors which influence the relationship between the psychosocial stressors and disease, which are-nature of stressors, number of stressors, how the stressors persists, person's own biological vulnerability, learned patterns of coping, etc.

Stressors are the sources of psychological stress, whose longer persistence can probably lead to mental disorders and may affect our health also, as it is clear from the literature survey, mentioned above. Like, a survey was done to determine the relation between 'stress and mental health among medical students', whose detailed information is mentioned below.

Psychological stress on mental health study: Studies of medical science expose medical students to many activities and situations, which enhance stress within their minds. If this stress, retains for a longer duration it adversely effects the mental health and as a result, further professional burnout occurs. This study aimed to find out the association of stress impact and adverse effects of medical studies with psychological distress among medical students. A cross-sectional study was done on a sample of 367 final year medical students of a medical college. Questionnaire was prepared for this research, which aimed to collect data about-socio-demographic data, self-reported health status, and, stressful influences of studies. Their mental health status was checked by General Health Questionnaire (GHQ-12). In the study, it was found that, 50% of the students, frequently felt, psychic tension and one-third of the students had Insomnia. Nearly one-half of the students had moderate to high levels of general stress. Exams were found to be a high level psychological stressor in 63.1% of the students. Communication with teaching staff was also reported as a stressful thing by one quarter of the examinees. The scores of GHQ-12 was found above threshold in 55.6% of all the students. The most common reasons for the mental health problems among students were found to be examinations and contact with their teachers. From this survey, it was concluded that, academic stress greatly affected the mental health of those students. For reduction of this stress, effecting their mental health, bringing about changes in examinations and teacher-student communication was essential [10].

The results of this survey, clearly underlines the fact that- "psychological stress is the root of many mental health problems." So, this research aimed to target the psychological stress to prevent or treat the mental health problems.

The literature survey on-impact of psychological stress on physical health, was also done. The description about the psychological stress on physical health is mentioned below.

Psychological stress on physical health: Some appraisal processes which is like a threat to us and which goes beyond our coping ability, leads to psychological stress. Neuroimaging research indicates that these appraisal processes which have its origin in the systems of the brain can also control the physiological stress reactions in our body. A few researches also tell that, also leads to the risk of development of physical disease within the body. There are also a few studies, which tells that, brain bases of stressor also enhanced the reactions associated with cardiovascular system and increased the risk of heart disease [11].

Many physical illnesses have psychological stress, as a common factor, associated with them. Psychological stress is identified as a risk factor, for the onset as well as the progress of various diseases. Some literatures suggest that stress play a role in causing type-2 diabetes mellitus also. Stress can not only result in the development of type-2 Diabetes Mellitus, but, can also negatively impact the patients of this disease.

Some epidemiological evidences also suggests that psychological factors may be considered as risks and may increase the chance for the development of some specific types of Cancer. They may also play important role in the aging process of cells. It is essential to understand the molecular mechanisms of stress interaction for managing and preventing Cancer. Psychological or psychosocial stress has been found as an important factor connected to beginning, progression and metastases of cancer. Emotional stress can also lead to progression of cancer.

Thus, it is quite clear that, psychological stress is not only, the root of various mental problems, but, it is also the root of the development and progress of various diseases associated with physical health. So, this root must be feeded with stress-relieving or happiness-promoting components, to prevent mental and physical health problems, as much as possible [12].

Phytochemicals

These are some bioactive components, which are produced and found naturally in plants. Different plants have varying presence and secretions of these components within them. Some classes of phytochemicals, such as- terpenoids, polyphenols, phenolic constituents, alkaloids, carotenoids, phytosterols, saponins and fibers, they effect human health, by many different mechanisms of actions, such as- they may exhibit antioxidant properties, effect of cell differentiation, they may increase enzyme activity, may cause detoxification also, they may also effect DNA metabolism, may also bring about an increment in detoxification of cancer cells, or may also reduce cell proliferation, etc. Since ancient time, in various parts of the world, people have been using these phytochemicals mainly for treatment purposes. These phytochemicals, not always, but in most cases, are safe to be used on a human body. Although, a few cases of toxicity and risk of diseases have also been reported, which are associated with these phytochemicals. There are several data available, regarding *in vitro* study of these phytochemicals. But, lesser data available about their *in vivo* studies.

The content mentioned above, collected from a literature survey, done on phytochemicals, clearly underlines the fact that- phytochemicals are mostly safe to be given to a human being. This fact motivated me to study about- one or more phytochemical components, which can serve as a therapeutic agent, against psychological stress or happiness promoting phytochemicals. After a few literature surveys from 'PubMed', got to know that- "green tea has a few phytochemicals, which effects mood and cognition." Thus, a strong hope raised, that, maybe those components of 'green tea (*Camellia sinensis*)' can be used, as a 'therapy or therapeutic vaccine' against psychological stress. Also, all of us know that, green tea is not only quite safe for our consumption, but, also very good for our health. Thus, its components are likely to be safe on human body, and, at the same time, are more likely to promote a good physical and mental health also, if administered into the human body. They may also be used as a part of the treatment of mental disorders and maybe some physical health issues also, by working on their root *i.e.*, 'psychological stress'. Thus, in the light of these hopes, using a few tools of bioinformatics, not only studied the chemistry of those components of green tea, but, also did their ADMET analysis, to predict their detailed pharmacokinetics and toxicity on a human body [13].

Research background

This research was done, to discover and study those phytochemicals, which can serve as a potential therapeutic vaccine against psychological stress and maybe potential preventive vaccine for prevention of mental disorders and some physical health issues also. To achieve this goal, this research mainly involves usage of practical application of bioinformatics. But, before getting deep into the, actual computational tools and methodology, this research used, it is first of all important for us, to explore the background knowledge, which motivated this research. A few background facts and informations are mentioned below.

Bioinformatics and medicine

We have been able to generate, various beneficial and useful biological data through various efforts, such as, human genome project and sequencing projects in other organisms. Bioinformatics can be useful for analyzing and interpreting these biological data. Thus, we can define Bioinformatics as “a discipline, which applies the computational tools and its analysis, for interpreting the biological data.” This interdisciplinary field encompasses all of these-computer science, mathematics, physics and biology. This field is very necessary for managing data in modern biology and medicine. Bioinformatics and its potential to interpret the biological data can be very useful to us in various ways, in the field of medicine, such as-deeply understanding the diseases, discovery and development of new drugs against various diseases, etc. [14].

In silico ADMET

There are many small molecules or chemical substances, in our world, by which our health can get effected. The examples of such substances are drugs, pesticides, food additives, chemicals used in industries and pollutants which cause environmental pollution. It is essential for us to know about, absorption, distribution, metabolism, excretion and toxicity of chemical compounds within our body, to assess their risk or safety in our body. Although, we can determine all of these, through various *in vitro* and *in vivo* methods also. But, those methods are quite expensive to afford and also demands hard work and time. Thus, *in silico* techniques are widely used, and can overcome these drawbacks. *In silico* techniques can predict all these properties for various chemical substances. Although, *in silico* techniques of ADMET analysis, also may have their own challenges and limitations.

In the last few years, there have been many developments in the technology of *in silico* ADMET analysis. Now, many of the ADMET properties can be calculated and some softwares can very accurately calculate the physicochemical properties, which are very close to experimentally measured data. However, more advancement may be required for better and more successful drug discovery and development.

NCBI portal

The portal of ‘NCBI (National Center for Biotechnology Information)’, <https://www.ncbi.nlm.nih.gov/> has many resources, facilities and databases, associated with it. It is a treasure of-research publications; information about genes, genomes, proteins, etc.; gene expressions; chemical compounds (PubChem); BookShelf, etc. It is a complete portal in itself for all bio-researchers [15].

The main literature surveys, from PubMed, which set up the main foundation and mainly motivated this research, were a few scientific publications, which declared that, “green tea components have the potential to improve our mood and cognition.”

Since several years, green tea (*Camellia sinensis*), has been used as beverage. There are a number of claims about its benefits also. Study has been done to determine its effects on human brain also. The study provided evidence that green tea positively effects the psychopathological symptoms, such as reduces anxiety, can provide improvement in memory and attention and also it can improve the working of the brain. MRI has captured that green tea has the ability to activate the working memory. It was found that ‘L-theanine’ and ‘Caffeine’, both separately and in combined form had influence on brain and its functions. It is traditionally known and believed that, green tea induces mental clarity, cognitive function, physical activation and relaxation. Recently, a special type of green tea, known as ‘matcha tea’, is becoming popular in all over the world. It is frequently referred to as mood and brain food. This tea has higher amount of green tea phytochemicals as compared to regular green tea. Some researchers have been done on these components of green tea ‘caffeine’, ‘L-theanine’, and, ‘Epigallocatechin Gallate (EGCG)’, to determine their effects on mood and cognition. These effects were studied with the separate intake of these components as well the combined intake of these components. It was reported that, caffeine mainly improved performance on demanding long duration cognitive works, self-reported alertness, arousal and vigor. Significant effect of this component was observed at low dose of 40 mg. L-theanine, at the dosage of 200 mg was observed to improve self-reported relaxation, tension and calmness. L-theanine and caffeine, in combination was found to improve performance in attention-switching activities and alertness, but relatively lesser than caffeine alone did. No conclusive evidence was found about the effect of EGCG on mood, cognition and brain. Thus, the studies, provided evidence that caffeine

clearly has positive influence on attention, memory and suppression of distraction. L-theanine, on the other hand, induces relaxation and opposes arousal brought about by 'caffeine'.

Utilizing the above-mentioned scientific facts as foundation, this research mainly involved, further deep study and analysis of 'Caffeine' and 'L-theanine', to predict whether they can be successfully and safely used as the therapy of psychological stress and mental disorders or not [16].

Databases and tools

Some of the databases and tools used in this research are mentioned below:

PubMed: It is a database, which help us to search and retrieve, many scientific publications, associated with biomedical and life sciences. It has the goal of improving human health-from personal level to global level. This database contains, more than 36 million citations and abstracts of biomedical literature. It doesn't contain full-text journal articles. However, it may have the link to full text, when contents are available from other sources, such as 'publisher's website' or 'PubMed Central (PMC)'. Since 1996, it is available to the public on internet. This database was developed and maintained by 'National Center for Biotechnology Information (NCBI)' at the U.S. 'National Library of Medicine (NLM)' located at 'National Institute of Health (NIH)'. The scientific publications available on this database are mainly associated with-biomedical field, health, life sciences, behavioral sciences, chemical sciences and bioengineering. There are various components of this database also, such as-MEDLINE, PubMed Central and Bookshelf [17].

In this research, some abstracts on PubMed has provided this foundation scientific knowledge that, "green tea components can affect our brain, mood and cognition." This fact has been further analyzed and studied in this research. Other than this, 'PubMed' has provided many more valuable scientific abstracts, which are mentioned in this research article.

PubChem: It is an open, chemistry-based database at 'National Institute of Health (NIH)'. Anyone can provide or update scientific knowledge in this database and other researchers may use that updated information. It was launched in 2004. Many scientists, students and general public can collect chemistry related informations from this database. Millions of people throughout the world use this database or website for various purposes. It mostly contains data about small molecules, but, it also has data about some large molecules, such as nucleotides, carbohydrates, lipids, peptides and chemically modified macromolecules. It provides information about-chemical structures of molecules, their identifiers, their physical and chemical properties, their biological activities, their safety and toxicity data, etc. This database gets data from various sources-government agencies, chemical vendors, journal publishers and more. This platform is ever-growing. By going through PubChem statistics page we can get to know about the latest data count on this database [18].

In this research, 'PubChem' has been used for collecting information about chemistry, properties and pharmacological aspects, etc. of 'Caffeine' and 'L-theanine'. The data available on PubChem provided the evidence that these two molecules can serve our desired purpose.

Drugs.com: It is the largest, most visited website, which provides information about diseases and medicines. The goal of this platform is to be the most trusted internet's resources, which provide information related to drugs and health. It tries to provide independent, objective, comprehensive and up-to-date information with clarity and concise way. This information can be used by, customers and healthcare professionals, both. This database gets its information from various sources, such as American society of health-system pharmacists, Cerner Multum and Micromedex. It also provides information on health, which it gets from various sources, such as-Harvard health publications, Mayo clinic, etc.

In this research, drugs.com has been used to gather knowledge about mental disorders, their therapies and their medicines, whose description is mentioned in the 'Introduction' part of this research article.

ADMETlab2.0: Many novel drug candidates fail after their development, due to their failure at the level of pharmacokinetics and toxicity. Absorption, distribution, metabolism, excretion and toxicity of the chemical substances must be checked and determined as early as possible. ADMETlab2.0 is an advanced version tool of ADMETlab, which is a widely used bioinformatics tool for determining the ADMET properties as well as physicochemical properties of various chemical substances. ADMETlab2.0 has relatively better capacity to help medicinal chemists in the research and development of drugs. This advanced version has-comprehensively enhanced ADMET profiles, re-engineered modules and batch evaluation support, robust and accurate MGA models, practical

explanation and guidance. It mainly has two facilities of ADMET analysis-ADMET evaluation and ADMET screening. It provides information about 13 properties related to medicinal chemistry; 23 properties associated with absorption, distribution, metabolism and excretion; 27 endpoints related to toxicity; 8 toxicophore rules-about the searched component. It is available to the researchers, free of cost and doesn't require any registration also to be accessed.

In this research, using this tool, physicochemical and ADMET properties of 'caffeine' and 'L-theanine' have been analyzed. Both of them have been found to be overall safe on the human body in this research [19].

Methodology

Aim: To study and analyze the structure, chemistry, and, pharmacological aspects of 'Caffeine' and 'L-theanine' from PubChem [20].

Protocol:

- Opened 'google chrome' browser.
- Opened 'PubChem' in this browser.
- In the search box, one by one, typed the names-'Caffeine' and 'L-theanine'.
- Clicked on the topmost results of Pubchem, shown on the screen, as a result of both of my search.
- Studied and analyzed their-2-dimensional and 3-dimensional structures, physical and chemical properties, drug and medication information and pharmacology and biochemistry, one by one. Didn't get any 'drug and medication information' about 'L-theanine'.
- Saved their canonical smiles structure in an M.S.Word file, for further study.
- Took the screenshots of study and analysis done from PubChem.

Aim: To compute the physicochemical and ADMET properties of 'Caffeine' and 'L-theanine' using ADMETlab2.0.

Protocol:

- Opened 'google chrome' browser.
- Opened 'ADMETlab2.0' in this browser.
- Then, clicked on 'GET STARTED' button, below 'ADMET screening' option, shown on the portal.
- Then clicked on 'enter a list of SMILES' option.
- Then, in the box, which showed up, entered the 'canonical SMILES' structures (saved in word file) of both 'caffeine' and 'L-theanine' together.
- Then, clicked on the 'submit' button and submitted the canonical SMILES structures of both the molecules.
- This online tool computed the properties of both the molecules together and provided the computed results for both the molecules.
- Then, clicked on the 'view' buttons, to analyse the computed results of both 'caffeine' and 'L-theanine' separately.
- Analyzed the computed properties for both the molecules. Studied physicochemical properties, medicinal chemistry, absorption, distribution, metabolism and excretion.

RESULTS

PubChem analysis

The results show in Figures 1-18.

Caffeine:

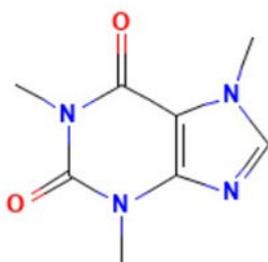


Figure 1 Two-dimensional structure of ‘Caffeine’

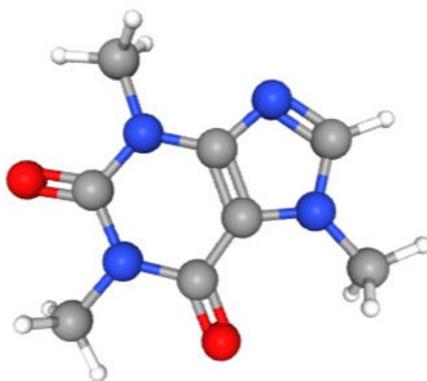


Figure 2 Three-dimensional structure of ‘Caffeine’

Property Name	Property Value	Reference
Molecular Weight	194.19 g/mol	Computed by PubChem 1.1 (PubChem release 2021.05.07)
MW:1	194.19	Computed by InChI 1.0.6 (PubChem release 2021.05.07)
Hydrogen Bond Donor Count	0	Computed by Cactus 3.4.0-16 (PubChem release 2021.05.07)
Hydrogen Bond Acceptor Count	3	Computed by Cactus 3.4.0-16 (PubChem release 2021.05.07)
Rotatable Bond Count	0	Computed by Cactus 3.4.0-16 (PubChem release 2021.05.07)
Exact Mass	194.080159 g/mol	Computed by PubChem 1.1 (PubChem release 2021.05.07)
Monoisotopic Mass	194.080159 g/mol	Computed by PubChem 1.1 (PubChem release 2021.05.07)
Topological Polar Surface Area	35.43 Å²	Computed by Cactus 3.4.0-16 (PubChem release 2021.05.07)
Heavy Atom Count	14	Computed by PubChem
Formal Charge	0	Computed by PubChem
Complexity	298	Computed by Cactus 3.4.0-16 (PubChem release 2021.05.07)
Isotope Atom Count	0	Computed by PubChem
Defined Atom Stereocenter Count	0	Computed by PubChem
Undefined Atom Stereocenter Count	0	Computed by PubChem
Defined Bond Stereocenter Count	0	Computed by PubChem
Undefined Bond Stereocenter Count	0	Computed by PubChem
Covalently-Bonded Unit Count	1	Computed by PubChem
Compound is Chiral	No	Computed by PubChem release 2021.05.07

Figure 3 Physical and chemical properties of ‘Caffeine’ on PubChem

pubchem.ncbi.nlm.nih.gov/compound/2519#section=Drug-and-Medication-Information

7 Drug and Medication Information

7.1 Drug Indication

Caffeine is indicated for the short-term treatment of apnea of prematurity in infants and off-label for the prevention and treatment of bronchospasm/dyspnea caused by premature infants. In addition, it is indicated in combination with sodium bicarbonate to treat respiratory depression resulting from an overdose with CNS-depressant drugs. Caffeine has a broad range of over-the-counter uses, and is found in energy supplements, athletic enhancement products, pain-relief products, as well as cosmetic products.

7.2 LiverTox Summary

Caffeine is a xanthine alkaloid that occurs naturally in seeds, leaves and fruit of several plants and trees that acts as a natural pesticide. Caffeine is a major component of coffee, tea and chocolate and in humans acts as a central nervous system (CNS) stimulant. Consumption of caffeine, even in high doses, has not been associated with elevations in serum enzyme elevations or instances of clinically apparent liver injury.

7.3 Drug Classes

CNS Stimulants, Xanthine Derivatives

7.4 FDA Approved Drugs

103 items

Figure 4 Drug and medication information about ‘Caffeine’ on PubChem

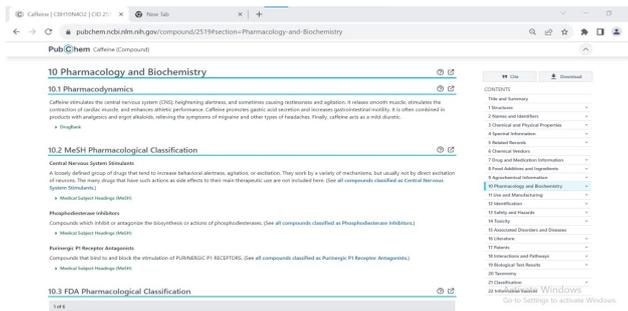


Figure 5 Pharmacology and biochemistry of ‘Caffeine’ on PubChem

L-theanine:

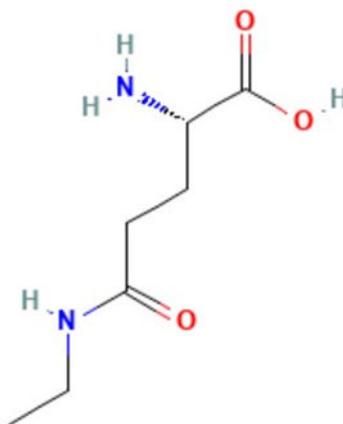


Figure 6 Two-dimensional structure of ‘L-theanine’

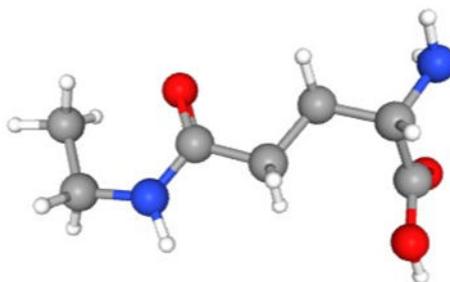


Figure 7 Three-dimensional structure of ‘L-theanine’

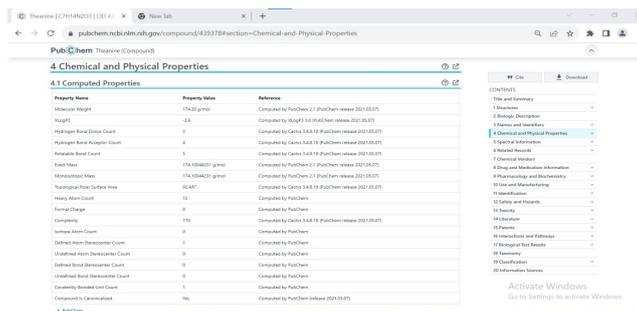


Figure 8 Physical and chemical properties of ‘L-theanine’ on PubChem

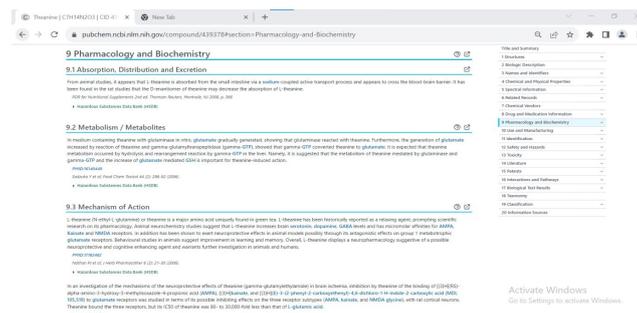


Figure 9 Pharmacology and biochemistry of ‘L-theanine’ on PubChem

ADMET analysis

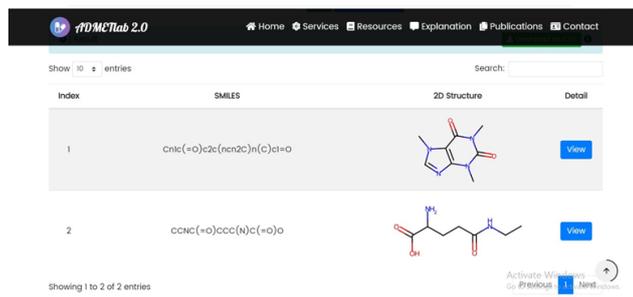


Figure 10 Computation results display of ‘Caffeine’ and ‘L-theanine’ by ADMETLab2.0

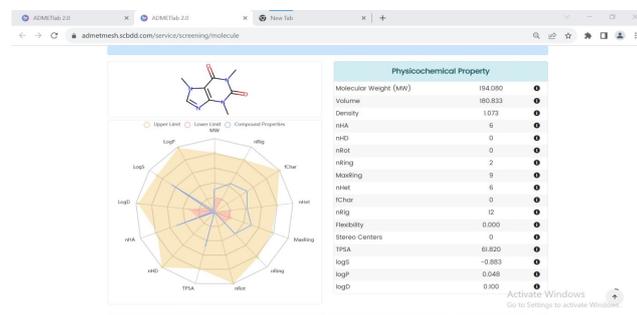


Figure 11 Physicochemical property computation of ‘Caffeine’ by ADMETLab2.0

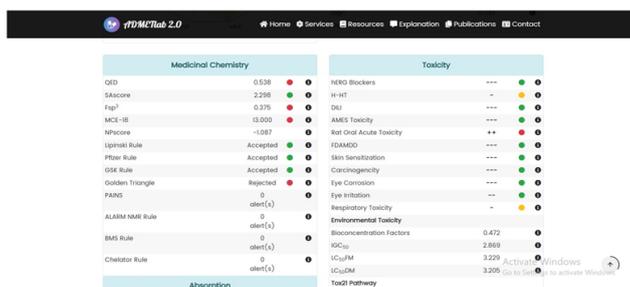


Figure 12 Medicinal chemistry and toxicity analysis of ‘Caffeine’ by ADMETlab2.0

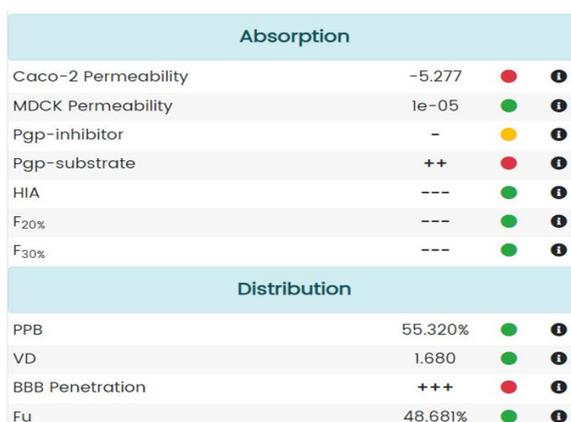


Figure 13 Absorption and distribution analysis of ‘Caffeine’ by ADMETlab2.0

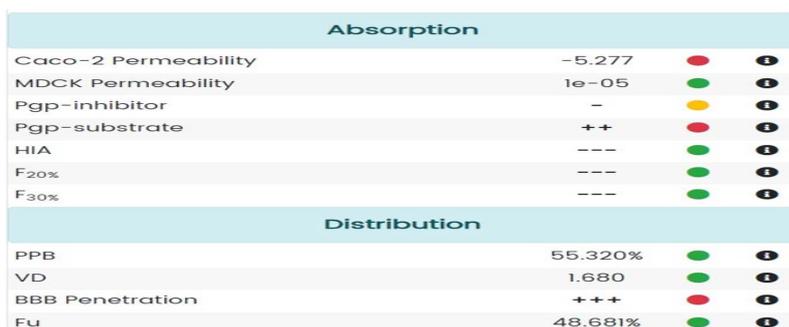


Figure 14 Metabolism and excretion analysis of ‘Caffeine’ by ADMETlab2.0

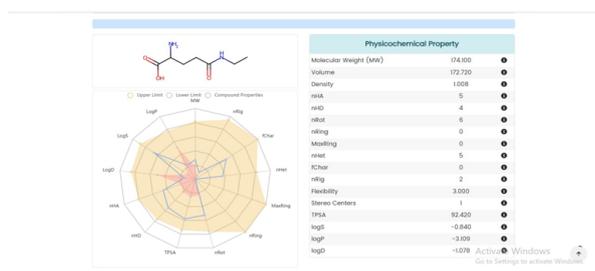


Figure 15 Physicochemical property computation of ‘L-theanine’ by ADMETlab2.0

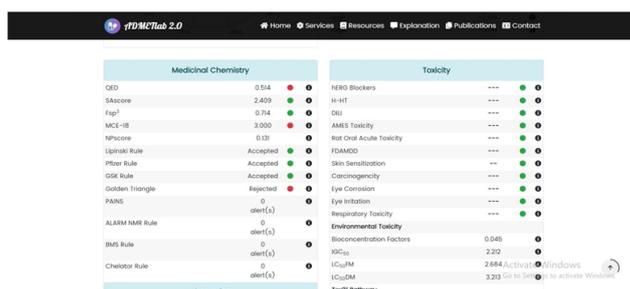


Figure 16 Medicinal chemistry and toxicity analysis of ‘L-theanine’ by ADMETlab2.0

Absorption			
Caco-2 Permeability	-5.842	●	ⓘ
MDCK Permeability	0.0026	●	ⓘ
Pgp-inhibitor	---	●	ⓘ
Pgp-substrate	---	●	ⓘ
HIA	---	●	ⓘ
F _{20%}	---	●	ⓘ
F _{30%}	---	●	ⓘ
Distribution			
PPB	6.315%	●	ⓘ
VD	0.377	●	ⓘ
BBB Penetration	++	●	ⓘ
Fu	90.412%	●	ⓘ

Figure 17 Absorption and distribution analysis of 'L-theanine' by ADMETlab2.0

Metabolism			
CYP1A2 inhibitor	---		ⓘ
CYP1A2 substrate	---		ⓘ
CYP2C19 inhibitor	---		ⓘ
CYP2C19 substrate	---		ⓘ
CYP2C9 inhibitor	--		ⓘ
CYP2C9 substrate	--		ⓘ
CYP2D6 inhibitor	---		ⓘ
CYP2D6 substrate	--		ⓘ
CYP3A4 inhibitor	---		ⓘ
CYP3A4 substrate	---		ⓘ
Excretion			
CL	5.609	●	ⓘ
T _{1/2}	0.712		ⓘ

Figure 18 Metabolism and excretion analysis of 'L-theanine' by ADMETlab2.0

DISCUSSION

A few abstracts on 'PubMed' claimed that, green tea has the potential to improve our mood and cognition. Specially, two phytochemicals, 'caffeine' and 'L-theanine', have this potential to a great extent. 'Caffeine' can improve alertness, memory, etc. and L-theanine can promote relaxation and calmness. Thus, got the evidence that, if they are separately or in combination, administered into a human body, they can cure 'psychological stress', which is the root cause of various mental disorders, and, onset and progression of some physical health issues also. But, before jumping to any conclusion, I decided to study them deeply using 'PubChem' and 'ADMETlab2.0'. I analyzed their-2D and 3D structures, physical and chemical properties, drug and medication information, and, their pharmacological aspects using 'PubChem'. 'Drug and medication information' about 'Caffeine' claimed that, it is already used as medication, for various problems, such as-apnea of prematurity in infants, bronchopulmonary dysplasia caused by premature birth, etc. Its 'pharmacodynamics' suggested that, it stimulates the Central Nervous System (CNS), enhance alertness and sometimes may also cause restlessness and agitation. It relaxes the smooth

muscles and stimulates the contraction of cardiac muscles. It can improve athletic performance also. On the other hand, 'L-theanine' increases the levels of serotonin, dopamine and GABA, thus promoting happiness and relaxation. Then, I decided to analyze the pharmacokinetics of these phytochemicals in the human body. For this purpose, I used 'ADMETlab2.0' to compute the ADMET properties of caffeine and L-theanine together. With the help of this tool analyzed the physicochemical properties, medicinal chemistry and ADMET properties of both these phytochemicals. This tool predicted that, both 'Caffeine' and 'L-theanine' follow Lipinski's rule, Pfizer rule, and, GSK rule. Thus, both of them are somewhat suitable as pharmaceutical drugs. Overall, both of them were predicted to be safe on human body, but, caffeine had red dots in front of rat oral acute toxicity, Caco-2 permeability, Pgp substrate, BBB penetration and CL, indicating itself as somewhat alarming entity towards all these. Similarly, L-theanine also had red dots in front of Caco-2 permeability, and, BBB penetration, indicating itself as somewhat alarming entity towards these. Although, this research finally concluded that-caffeine and L-theanine, either separately or together, can serve as 'preventive vaccines' to prevent mental disorders, or, 'therapeutic vaccines' to cure 'psychological stress' or 'mental disorders'. 'L-theanine' has to be the key component of such a vaccine [21].

CONCLUSION

'L-theanine' and 'caffeine', both together and separately, can positively influence a human brain. These are such phytochemicals, from green tea, whose intake or administration into a human body can not only prevents the mental problems, but, can also treat them. Also they are safe for human intake, as predicted by ADMETlab2.0. These phytochemicals from green tea, together or separately, can serve as both preventive and therapeutic vaccine for mental health. Specially, L-theanine has the best potential to serve as such a vaccine.

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