PHARMACOLOGICAL ROLE OFEUGENOL IN MANAGEMENT OF ANXIETY DISORDERS

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Abstract:

Anxiety is one of the prevalent conditions among the other psychiatric disorders. It is highly diagnosed but unfortunately its treatment is not parallel to its diagnosis. The Classical signs of anxiety, which are also the major contributor towards the development of anxiety are stress and fear condition. According to one estimate quarter of United states population suffered from anxiety with a point score scale of maximum 10 points. The major sources with high levels of stress are family burden, economy and poor working conditions, that has a great impact on physical and mental health. There are various theories behind the anxiety but its further complications are still debatable. The major aim in the treatment of General Anxiety Disorder is to reduce the symptoms and to improve the quality of life. There are number of pharmacological treatments are available in the management of anxiety but the risk of rebound anxiety limit their use. So, there is a need to introduce the new and potential agents to alleviate anxiety complications. Today, natural herbal medicine has gained high access towards the management of anxiety and their potential role cannot be neglected. Eugenol is isolated from many herbal medicines and reported to possess many pharmacological activities like antiseptic anticonvulsant, anti-inflammatory, anti-stress, antioxidant, anesthetic, antimicrobial and other CNS disorders. The current review highlight its pharmacological importance in the alleviation and management of anxiety and its complications

Keywords: Anxiety, Eugenol, Therapeutics, Herbal.

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Introduction

Anxiety is having 31% of life time prevalence and sad part is that the anxiety disorders are not treated and diagnosed well[1]. 3.1% which is 6.8 Million peoples of America are having anxiety disorders[2]. Classical fear condition is central to anxiety disorders etiology[3]. Anxiety conditions are chronic, costly, disabling, highly prevalent and mental disorders[4]. About a quarter of United states citizens have wide spread stress and it has termed as extreme level on 10 point scale having 8,9, or 10 points, the top source of levels of stress being family, money and work[5].The stress concept and assessment can be viewed by its sociological, psychological, environmental and biomedical perspective[6-8]. Because of that it is operationalized in a different way with psycho and social stress being considered as chronic strains, major life events, trauma and day to day hassle[9]. The Psychological stress/anxiety is interconnected with health behavior[10-11] and it is demonstrated as link to health consequences[12]. There are different studies showing relationship between unhealthy lifestyles which includes smoking and physical inactivity and work related stress in healthy populations[13-15]. A study on psychosocial stressors such as family issues, financial issues, working stress and relationship stress was investigated influence of smoking pattern in United states sample over nine and ten years, Subsequently adjustment for sex, socioeconomic status and age originated a relationship between high psychosocial stress and persistence of smoking[16]. Commonly analyzed outcomes of stress concern physical and mental health and the pathway of anxiety/stress leading to dysfunction and disease are not understood[17] cardiov ascular disease[18-19] Necrosis/Cancer[20] anxiety and depression[21-22].Treatment of GAD reduces its symptoms and disability also improving health-and life's quality, benzodiazepines like pregabalin and buspirone are used in the treatment, "Selective serotonin reuptake inhibitor (SSRIS)" and "Serotonin norepinephrine reuptake inhibitors (SNRIS)" are used as the first line treatment for GAD. The effectiveness of tricyclic antidepressants such as imipramine is similar to that of Selective serotonin reuptake inhibitor, but tricyclic antidepressants have a less favorable safety profile[23] (Stein *et al*., 2015).Clove oil is

been used since ancient time and it is used as an antimicrobial, antiseptic and antispasmodic in Chinese traditional medicine. Currently eugenol is widely used in household products, cosmetics, dental and pharmaceutical products, fragrance in soaps, flavoring substance for food and skin care products[24]. Eugenol is present in many herbs in medicine. It is an allyl chain substituted guaiacol (2- methoxyphenol)[25]. It is a clear to pale yellow oily liquid and is a member of the allylbenzene class of compounds; it is slightly soluble in water and organic solvents[26]. It is extracted from clove oil, nutmeg, bay-leaf and cinnamon and also derived from Eugenia caryophyllus, Myristicafragrans, and Laurusnobilis Linn etc[27]. It has antiseptic properties and it is used in perfumes, medicines and flavorings[28].It has anticonvulsant, anti-inflammatory, anti-stress, antioxidant, anesthetic, antimicrobial, anti-aggregatory activity and muscle relaxant properties[29-33] also it can be used in vaginal candidiasis treatment[34].In the models of animal it has also stated to have anesthetic and anti-inflammatory along with analgesic effects[35-36].It is also effective in reversing the short and long term memory[37].

Results and Discussions:

Garabadu*et al., 2011* reported that stress in the main psychopathological reasons for many mental disorders. Psychological and physiological responses to stress are moderated by SAS (Sympathoadrenal System), BMS (Brain Monoaminergic System) and HPA (Hypothalamic Pituitary Adrenal).by the regulation of the Voltage gated ion channels eugenol modulate brain functions and release of neurotransmitters. In this study they wanted to assess the eugenol anti stress effect in the rata by using 4 hour restraint model and ulcer index was used to for measuring as a parameterof response of stress. By estimating nor epinephrine and corticosterone SAS and HPA axis were monitored. For understanding of the role of BMS in the anti-stress effect of the eugenol analysis if dopamine, 5-HT and NE and their metabolites were performed in brain regions.NE, ulcer index and plasma corticosterone were increased by stress exposure and then eugenol pretreatment t for seven days reduced levels of NE, Ulcer index and plasma corticosterone which shows the better effects on the HPA axis. U shaped dose response curve was indicated by eugenol while reducing plasma corticosterone and ulcer index levels. Furthermore in all brain regions in 5-HT eugenolreversed the stress. Except hippocampus NE levels were also reversed in all of the brain regions. It was reported that eugenol has anti-stress activity by using 4 hour restrain models and the anti stress activity is due to BMS and HP, modulation[38].

PandianSelvan*et al., 2016*reported that eugenol is a class of allyl-benzene chemical, which is used in food products, and cosmetics. It is useful component of many medicinal herbs, it is antioxidant and pro-oxidant. It is also used in dental practices for reveling pain which arise from dentinal hypersensitivity and pulpitis. It has anti-conversant effect also. Due to lack of studies and data regarding effects of eugenol on CNS in the models of animals. Hence necessitates for extra research activities. The objective of this study was to evaluate and observe effects of eugenol in restrain stressinduced rats on motor co-ordination. Five groups were made with six animals per group. Group 1 was termed as Negative control, Group 2 was termed as Positive control, Group 3 was termed as treated with eugenol i.e. 150mg/kg body weight, group 4 was termed as restrain stress alone, group 5 was the treated group with eugenol and restrain stress also with 150 mg/kg body weight. They were given treatment for 15 days and on the end on 15th day rota road, plasma corticosterone, stair case behavioral parameter and narrow beam walk was measured. This study proved that they improve motor coordination in immobilization stress inducedwistarrats[39].

K. Tillisch*et al., 2012*reported that anxiety is characterized with Irritable bowel syndrome. **NK1R** system is concerned in the regulation of Pain and anxiety, which suggests a Potential therapeutic target in IBS. Their objective was determination of **NK1R** if inhibited will alter the scores of pain & response of brain to experimental anxiety and visceral pain symptoms in women's with irritable bowel syndrome or not. The type of study conducted was double blinded, cross over study and placebo controlled. The 11 subjects were involved in this study and out of them 8 provided fMRI data. AV608 in comparison with placebo, reduced anxiety was observed, pain ratings and negative effects. Decreased activity during visceral distention was observed with the treatment of AV608 by the anterior cingulate gyrus, hippocampus and amygdala. A decrease in the activity on the regions of brains was also related with interoception at anterior mid-cingulate gyrus and posterior insula and it was associated with AV608[40].

S. McLean et *al., 2005* reported that reports have found NK1 receptor antagonists role in the depression treatment. It has led to research in the substance P and NK1Rfunction in depression & anxiety. Initial distributions in brains areas have reviewed anxiety and depression. In preclinical data which was obtained for substance P and NK1R antagonist in the model (behavioral) of depression and genetically modified animals (phenotype). They lack the genes encoding for substance P and NK1R and this supports anxiolytic and antidepressant activity of NK1R antagonists & in some studies blockade of Neurokinin-1 receptor do not accounted the observed behavioral activity, clinical studies are mixture of failed, Negative and Positive studies on the antidepressant activity of Neurokinin-1 receptor antagonists[41].

AlexandreSurget*et al., 2008* reported that due to the dysfunction of HPA axis and changes in Hippocampus anxiety and depression disorders are linked. Unpredictable chronic mild stress (UCMS) could summarize these effects in a Model of mouse; anti-depressant treatment can reverse the down regulation of hippocampal

neurogenesis. It was concluded that hippocampal neurogenesis might thus be used by the monoaminergic ADs to counteract the effects of stress, whereas similar effects could be achieved by directly targeting the HPA axis and related neuropeptides[42].

SolmazMohammadinejad*et al., 2017* reported that eugenol is clove oil and obtained from Eugenia caryophylla buds and leaves. It is widely used in pharmaceuticals, cosmetic industry and food in limited concentrations also its derivatives used in medicine and anesthetics and local antiseptics. Eugenol is commonly used as antioxidants, anti-inflammatory, antimicrobial and anti-inflammatory .It is considered as safe but in recent years regarding toxicity a great concern has been shown. Although its genotoxicity and cytotoxicity studies are very controversial and limited[43].

Alline C *et al.*,2013 reported that daily tasks are affected that stress & Anxiety related illnesses which are severe psychiatric conditions. .Animal model of anxiety has helped in identification of many pharmacological mechanism and clinical effects of many drugs. It has revisited rodent models of stress & anxiety which are used globally. They have also defined the ethological which are light dark box tests, open filed and elevated plus maze, which assess unpunished & unlearned responses and vice versa are known as conditioned operant conflicts a test which isVogel conflict test. They have also discussed fear conditioning tests which is classical conditioning test. They have also defined the protocols which are used to induce stress (response) inrodents i.e. neonatal isolation stress and social defeat which are psychosocial, restrain stress which is physical and chronic unpredictable stress [44].

Catherine Belzung *et al.,* 2001reported that elevated maze plus and light dark choice and open field tests are used to measure anxiety like behavior tests. It can also be produced by a variety of threats like exposure to predator. When assessing behavior, it is important to increase the behavior paradigm variety which includes animal model of state and trait anxiety. It is necessary to state that such mice are animal models of a single dysfunction in gene rather than anxiety models. Balb/c mice display spontaneous elevated anxiety and it is more suitable model for pathological anxiety[45].

Michel Bourin*et al.,* 2007 reported that to study human pathologies animal model remains most used models and they answers unavailable questions from human patients to learn many mechanism of actions of drugs. First animal models for anxiety were developed with rats and then they were adapted with mixed success in mice. Mice are very easy to use with good genetic possibilities compared to rats. Both conditional and unconditioned models are described. Behavioral studies need solid care for parameters related with handling and paradigm environment. They also focused on re-exposure consequences to the apparatus. The Test-retest measures could bring novel responses which shall be intensely studied for re validation of whole paradigm as anxiety model[46].

Johanna M. Hoppe *et al.*,2018 reported that substance p and NK1R modulates anxiety & stress related performance in animals studies, its alteration are also detected in human's anxiety illnesses but very little information is known regarding this system & individual differences in traits (personality) which are related with anxiety which includes trait anxiety, extraversion and neuroticism. Explorations of this relation can neurobiological underpin human anxiety behavior and its etiology of disorders. In this study the association between central NK1 receptor availability and measures (self-rated) of trait anxiety, extraversion and neuroticism were examined with amygdala being chosen as primary interest region because it suggests medicating effects of SP-Nk1 system on anxiety. They measured seventeen healthy individuals with the radiotracer [11C] GR205171 and positron emission tomography and Nk1 receptor and anxious trait was determined. A positive association was found between Neurokinin-1 Receptor & trait anxiety by voxel-wise analyses, and for neuroticism and trend in similar direction was also detected, subsequently extraversion was having negative association with them; extraversion was also in correlation negatively with NK1 measure fusiform gyrus and in precuneus/cuneus rendering to the whole brain analyses[47].

Mehta*et al* 2013reported that Eugenia caryophyllata is used in antiseptic, analgesic and dental care. The study was intended to investigate the clove oil outcome in depression & locomotion. FST and TST were used to measure depression. Animals treated with clove oil in FST duration of immobility was decreased but at quantity of 0.25 ml/kg it shown increase. TST also showed decrease in the immobility period by clove oil at three doses. The Photoactometer process shown increase in locomotor activity on 03 doses while significant ($P<0.05$) only at 0.1 ml/kg. Rota rod tests shown enhanced muscle contraction at 0.1 ml/kg and significant increase ($P<0.05$) in the latency to fall from the Rota road in comparison with control group. At 0.025mg/kg,i.p it decreased the latency to fall compared to control group. Clove oil at 0.05ml/kg also shown reduction in the latency to drop from Rota rod but results was not significant statistically. Therefore it was resolved that the pretreatment with clove oil enhances locomotor activity and decrease depression similarly to those exhibited by psycho stimulant[48].

Mathieu Nollet*et al., 2013* reported that depression is a major problem affecting cognitive and physical impairment that leads to maladaptive behavior and it has high life time prevalence and it is necessary to have improved therapeutics and this requires animal model to investigate key biological correlates. The chronic mild stress (Unpredictable) model is described in this unit which is used as an antidepressant model. Originally it was used on rats and now it is also used in mice to take

advantage of this species as an experimental model which can study development components of depression, its etiology and identification of treatments which are novel[49].

Distler*et al.*,2012 reported that Glyoxalase system contains enzyme named Glyoxalase 1 (GLO1), it is a metabolic pathway which detoxifies αlpha Oxo aldehydes chiefly methylglyoxal. Methylglyoxal is predominantly made by breakdown of glycolytic (intermediates), dihydroxyacetone phosphate and glyceraldehyde 3 phosphates. Glyoxylase-1 expression is also related with anxiety behavior. A casual role or glyoxalase-1 in anxiety behavior by using viral vectors for over expression in the anterior cingulate cortex was found and it was found that local glyoxalase-1 over expression increased anxiety behavior[50].

Ul'yana et *al* 2013 reported that evidence suggesting that serotonergic system in the brain plays role in controlling of chronic social stress defeat, depression & anxiety. They studied while analyzing the mRNa levels in the ralph nuclei of serotonergic levels in midbrain which can be associated with chronic social defeats in male mice in special experimental settings.Tph2,Moao,Htr1a and sert were the serotonergic genes along with studies on creb genes and Bdnf. While compared to control group the that mRNA levels of Tph2,Moao,Htr1a &sert genes, creb genes and Bdnf in Ralph nuclei of defeated mice are reduced and expression of above mentioned genes were not restored even after two week relative rest. But some up regulations detected in loser (rested). CSDS experience inducing the development of mixed anxiety/depression-like state in male mice down regulates the expression of serotonergic genes along with creb&bdnf genes associated with the synthesis, inactivation, and reception of serotonin [51].

Yan-Mei Liu et al 2019 reported that central amygdala plays important role in emotional behaviors expression. This study stated that the inhibition of GABAergic in central amygdala was increased significally by methyl eugenol .The methyl cellulose with the help of electro-physiologic recordings showed that it increase miniature inhibitory post synaptic currents in central amygdala slices and also tonic currents but not affecting miniature excitatory postsynaptic currents. The central amygdala specific infusions and intraperitoneal injections in the fear induced anxiety animal models of methyl cellulose, they reduced anxiety related behaviors in mice due to activation of $GABA_AR$s (A-type GABA receptor) and because of that it is revealed that A-type GABA receptor in the central amygdala could be a potential goal for anxiety treatment and the methylcellulose is also able to enhance the GABAergic inhibition in central amygdala neurons for neuronal excitability inhibition[52]

Conclusion: It is evident that Eugenol has anti-stress activity by reducing activity of different neurotransmitters.

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