

Effect of Sigma Receptor Ligands In Hypertension

NavpreetKaur, HarpreetKaur, InduMelkani

Lovely School of Pharmaceutical Sciences, Lovely Professional University

Email ID: navpreet.24965@lpu.co.in

ABSTRACT

Hypertension is now described as a progressive cardiovascular syndrome. It is an escalating cardiovascular syndrome generally characterized by cardiac and vasculature abnormalities that targets major organs that include heart, brain, kidney which often leads to coronary heart disease, cardiovascular and renal disease. As of 2008, approximately, 28% or 978 million of the population of the world have hypertension. It is estimated that by 2025 hypertensive patients worldwide will increase to more than 1.56 billion. A novel approach to cure cardiovascular diseases particularly hypertension is the involvement of sigma receptors. The sigma receptor and its ligands have been implicated in a myriad of cellular functions, biological processes and diseases. Whereas the precise molecular mechanism of sigma receptor and their involvement in cardioprotection have not been elucidated. An interesting possibility is that sigma receptor could produce beneficial cardioprotective effects by modulating ion channels and suppression of cascade dependent apoptosis. Other mechanisms of sigma receptor action particularly sigma 1 receptor may involve increased Akt activity and improvement of impaired e NOS expression and phosphorylation and upregulation of sigma 1 receptor. Although more research is needed to further define the molecular physiology of sigma receptors, their involvement in the cellular pathophysiology of hypertension raises the possibility that sigma ligands could be useful as novel therapeutic agents.

INTRODUCTION

Hypertension is conventionally defined as the chronic medical condition as a result of persistent potentiation of blood pressure in systemic arteries. Systolic as well as diastolic pressures are measuring units to express the blood pressure. Resting blood pressure in healthy adults is within the limits of 100-130 mm Hg for systolic pressure and 60-80 mm Hg diastolic pressure. On the other hand, the blood pressure above the range of 130/80 mm Hg or 140/90 mm Hg, is considered as high blood pressure. However, certain changes were made in the explanation of hypertension by the American society of hypertension. Hypertension is now described as a progressive cardiovascular syndrome. It is an escalating cardiovascular

syndrome generally characterised by cardiac and vasculature abnormalities that targets major organs that include heart, brain, kidney which often leads to coronary heart disease, cardiovascular and renal disease. Blood pressure is considered as a parameter for hypertension.[1, 2]

CLASSIFICATION OF HYPERTENSION

Hypertension classification is done by assessing total cardiovascular risk which is done by evaluating blood pressure in comparison to the other cardiovascular disease markers. Parameters evaluated to classify hypertension include elevated blood pressure, various risk factors of cardiovascular disease and certain tissue markers. Cardiovascular risk factors include: age (especially old age), chronic kidney disease, obesity, dyslipidemia, excessive smoking, family history, diabetes and stress. Disease markers: widened pulse pressure, exaggerated blood pressure responsiveness to various exercise or mental stress, left ventricular hypertrophy(mild), increased pressure while atrial filling, decreased in time duration for diastolic relaxation, endothelial dysfunction, small artery stiffness, elevated serum creatinine, microalbuminuria.

STAGES OF HYPERTENSION

Hypertension is mainly classified into stage 1 , stage 2 and stage 3 hypertension. The stages are based on American society of hypertension, according to which the normal: Systolic pressure needs to ranging between 120 and 139 mm Hg and diastolic range between 80 and 89 mm Hg. This is the normal resting average blood pressure level in adults.

HYPERTENSION STAGE 1: If the systolic pressure fall in range from 140 to 159 mm Hg or diastolic pressure range fall 90 and 99 mm Hg, it is considered to be in stage 1 hypertension. In this stage, several cardiovascular risk factors are involved but no target organ damaged has been observed.

HYPERTENSION STAGE 2: In this stage the systolic pressure increased to 160 or higher or diastolic pressure is also higher i.e 100 or more, In this stage, many cardiovascular risk factors and clearly observed early disease markers are present. This stage is mainly identified by the presence of early signs of target organ damage.

HYPERTENSION STAGE 3: This is an advanced and severe stage of hypertension. Characterised by sustained resting blood pressure levels 140/90 mm Hg, and marked high

elevations levels of blood pressure to 160/100 mm Hg are common. All individuals with clinical evidence of target organ damage or CVD are included[2, 3].

SELECTED CAUSES AND RISK FACTORS OF HYPERTENSION

The main cause of hypertension is the chronic kidney disease. Kidneys are the major organs that provide a vital role in the maintaining the blood pressure in an individual. Disorder or disease of kidneys poses a threat to the cardiovascular health. Chronic kidney disease is a major cause of deaths related to cardiovascular diseases particularly hypertension. Hypertension can be either a causative factor of kidney disease or it can occur as a result of kidney disease. As per the data collected in the national survey of USA, patients with hypertension with chronic kidney disease are more as compared to the patients with hypertension without kidney disease. The survey results showed that individuals without chronic kidney disease accounts for only 23.3% of the hypertensive patients whereas patients with chronic kidney disease in stage 1 hypertension were found to be 35.8%, in stage 2 it was 48.1%, in stage 3 it was 59.9% and in stage 4 and 5 it was around 84.1% of the hypertensive patients. It is clear from the above survey results that occurrence of hypertension is more in patients common in people suffering from chronic kidney disease. Moreover cause of chronic kidney disease also influences the occurrence of hypertension [4, 5].

Obesity is one of the major risk factor for chronic arterial hypertension. Even though the connection among weight problems and high blood pressure is properly mounted in children and adults, the mechanism by means of which obesity directly reasons hypertension is underneath investigation. Activation of the sympathetic nervous system (SNS), the high amount of intra-abdominal and intra-vascular fat, sodium retention leading to increase in renal reabsorption, and the renin-angiotensin system, are major reasons associated with the pathogenesis of obesity-associated hypertension[1].

Excessive smoking also leads to hypertension. There is an acute effect of cigarette smoking on hypertension which is mainly produced by activation of sympathetic nervous system due to which there is an increase in concentration of catecholamines in plasma along with blood pressure increase. According to studies, it has been reported that increase in blood pressure lasts for more than 15 minutes after smoking 1 cigarette [6].

Studies reported that 26.4% of the total adult population in 2000 had hypertension which was predicted to increase by 60% in 2025. According to Framingham heart study, 90% of

subjects who had normal blood pressure at age 55 subsequently developed hypertension. Clinical studies also reported that in year 1995 to 2005 deaths due to hypertension was increased by 25.4% and the major reason was increasing prevalence of hypertension in the elderly. [7,8]

SIGMA RECEPTORS

Sigma receptors had been first identified by Martin and coworkers in 1976. Although they were initially identified as a subtype of opioid receptor, today they are considered as separate receptor proteins having their own mechanism of action, anatomical distribution and drug selectivity pattern. Sigma receptors are located in the brain specifically in the limbic and motor regions, in the peripheral organs (lungs, heart, digestive tract, immune system, reproductive system and excretory system) and also in monoaminergic and glutaminergic neurons in the body where they regulate synthesis and release of neurotransmitters. Drugs found to show affinity for sigma receptors include antihistamines, opioids, neuroleptics, anaesthetics, antidepressant drugs, synthetic ligands and endogenous sigma ligands. Sigma receptors are primarily of two types, sigma-1 and sigma-2 [10].

SIGMA 1 RECEPTORS

Sigma receptors are known to be chaperone proteins located in the mitochondrion associated ER membrane that regulate dendritic spine formation and regulate IP3 receptor in order to control calcium signalling between the ER and mitochondria. Sigma receptor has 2 transmembrane domains that are hydrophobic alpha helices. Sigma receptor also has a third hydrophobic helix that is associated with the ligand binding site for the agonist cocaine. Under some cellular conditions the sigma receptor can dissociate from mitochondria associated ER membrane and translocate to other parts of the cell to act as intracellular signalling molecules. When bound by specific ligands called agonists or when ER is under extreme cellular stress sigma receptor dissociates from mitochondrion associated ER membrane and can translocate to different parts of the cell. Common agonists that cause the sigma receptor to dissociate from mitochondrion associated ER membrane include psychostimulant such as cocaine, opioid pentazocine. Ligands called antagonist can bind and inhibit the dissociation and translocation of sigma receptor. When sigma receptor translocates they can bind to a number of different protein structures on the plasma membrane that affect both internal excitation and synaptic excitation. Internal excitation is effective when sigma receptor binds either directly or indirectly to voltage gated ion channels. [11]. Sigma-1

receptors either mediate acute or chronic action at the cellular level like the modulation of ion channels [12]

Figure 1: Sodium voltage gated ion channels

As shown in the diagram, sodium is heavily concentrated extracellularly and therefore rushes into the cell on opening of voltage gated sodium channels. However when voltage gated sodium channels are blocked flow of sodium into the cell is cut off and it is impossible for threshold to be reached and for an action potential to elevate. Voltage gated sodium channels can be inhibited both directly by the binding of sigma receptor and indirectly by sigma receptor through the activation of G protein receptor and protein kinase C. With these effects sigma 1 receptors can decrease sodium channel current as well as decrease sodium channel availability in order to decrease action potential firing. However there are multiple components contributing to the excitability of a neuron. Both potassium and calcium channels also influence internal neuron. Sigma 1 receptors have been shown to inhibit voltage gated potassium channels which should depolarize the cell and create an excitatory response therefore the opening of voltage gated potassium channels causes the cell membranes to become hyperpolarized and decreases the chance of an action potential. Gated calcium channels are more complex than sodium and potassium because calcium is involved in the release of neurotransmitters and also act as a second messenger molecule to trigger intracellular signalling pathways. Thus the opening of gated calcium channels and movement of calcium into the cell is associated with both release of neurotransmitters and intracellular signalling pathways. However sigma 1 receptors have been shown to both inhibit and facilitate the flow of calcium through gated calcium channels with all of these voltage gated ion channels being mediated at the same time by sigma 1 receptor, the overall picture is very complex and no studies have come up with a rule for the intrinsic excitability effects of sigma

1 receptor instead it has been shown the sigma 1 receptor have different effects in neurons located in different sections of the brain. This is likely due to changing concentrations of voltage gated channels as well as differential regulations of gated calcium channels. [9,11]

SIGMA 2 RECEPTORS

Sigma 2 receptors are not well established as compare to the σ -1 receptor one of the reason being lack of σ -2 selective agents. High amount of sigma 2 are located in liver and kidney and also present in tumor cell lines derived from various tissues, including melanoma and carcinoma cell lines of breast, prostate and lung. Researchers identified the details about sigma 2 receptors mainly in the field of tumour biology therefore most of the sigma ligand show positive effects as anticancer therapy. For the sigma 2 receptor only one study till date conducted which identify that sigma agonist inhibit inward movement of potassium in the heart [12].

SIGMA RECEPTOR LIGANDS

Both the sigma receptors exhibit different binding profile which is the characteristic feature to distinguish between both the receptors. As revealed by pharmacological binding studies sigma receptors are the targets for a wide range of drugs. For a molecule to possess high affinity towards sigma receptors, it should have Atleast one basic nitrogen atom WHICH IS separated from an aromatic ring by 2 methylene groups and lipophilic bulky substituent. Some of the compounds that possess high affinity towards sigma receptors include: Benzomorphans, Phenothiazines, morphinans, phenylpiperidines, guanidines, butyrophenones and neurosteroids.

Both the sigma receptor subtypes have their own selective ligands. Sigma1 receptor shows high affinity to dextrorotatory isomers whereas sigma 2 receptor show affinity to levorotatory isomers. Various agonists and antagonists at sigma 1 receptor had been identified. It includes various classes of drugs like Antipsychotic drugs (example include haloperidol, risperidone), Antitussives (example include dextromethorphan, carbetapentane), Addictive drugs etc. However for sigma 2 receptor, few pharmacological data is available.[10]

Table :Various agonists and antagonists at sigma receptors include:

S.NO.	Agonists	Antagonists
1	Afobazole	AC927

2	Arketamine	AHD1
3	Anavex-273	UMB116
4	BD1052	YZ-069
5	BD1031	UMB103
6	Berberine	UMB101
7	Cocaine	Sertraline
8	Dihydroepiandrosterone	S1RA(E-52862)
9	Dihydroepiandrosterone sulphate	Rimcazole
10	Dextromethorphan	Progesterone
11	Fluvoxamine	Panamesine
12	Fluoxetine	NE-100
13	Ketamine	MS-377
14	PRE-084	LR172
15	Siramesine	LR132
16	Lamotrigine	Haloperidol
17	Memantine	E-5842

EFFECT OF SIGMA RECEPTORS IN HYPERTENSION

Sigma receptor plays the important role in the regulation of the cardiovascular system. Sigma receptors agonist mainly causes the modulation of autonomic neurons in cardiovascular system. Only sigma-1 receptor among both the receptors has been cloned in human. Sigma receptor was initially discovered for their potential actions as antipsychotic drug. Sigma receptors are not only found central nervous system, but in others tissues also such as, endocrine, immune, and gastric system. In cardiovascular system myocytes is the location for binding of sigma ligands in neonatal and adult rats. Sigma ligands usually cause the increase in contraction by increasing the amount of calcium influx. It has been shown that sigma receptor antagonist.[10]

ROLE OF Fisetin

Fisetin is a polyphenolic compound having a wide range of pharmacological activities. Earlier, fisetin was considered to possess antioxidant, anti-inflammatory, anticancer and neuroprotective properties. But recently studies have proved that it also possess potent

cardioprotective activity. Fisetin affects smooth muscle contractility via increased nitric oxide generation and increased entry of calcium which activates the apoptotic pathway. Therefore it can be used as a better antihypertensive. Administration of fisetin also diminishes the apoptotic nuclei and reduces the expression of apoptotic proteins such as TNF- α , Fas L, FADD, Cleaved caspase-3 and PARP as well as increases the cell survival and anti-apoptotic proteins. [13]

ROLE OF AFOBAZOLE

Anxiolytic drug afobazole possesses cytoprotective action. Clinical researchers have identified ligand interactions of afobazole with MT1, MT3, Sigma1 receptor and MAO A. The cytoprotective effect is mainly due to its ligand molecule affinity towards sigma 1 receptor and MT3 receptors. This mechanism was studied by researchers using model of menadione genotoxicity. Experiment was conducted on single cell suspension extracted from bone marrow of male mice. The results of the experiments demonstrated that Afobazole decreased menadione induced DNA damage therefore studies provide that afobazole possesses cytoprotective action. [14]

ROLE OF SSRIS

Depression and cardiovascular diseases are interrelated. The occurrence of symptoms of depression in a patient with cardiovascular diseases is a major cause of concern these days. Prevalence of symptoms of depression in cardiovascular diseases can often worsen the condition and can make the disease more severe which can lead to death. According to the reports of New York Heart Association, on the occurrence of symptoms of depressive in the failure of heart, Class IV had the highest incidence of depressive symptoms with 42% of the total, then Class III with 38%, 20% was seen in Class II and finally 11% in Class I. Therefore treatment with SSRI's is considered to be effective in such cases of cardiovascular diseases. SSRI's are considered safe for patients with cardiovascular diseases. SSRI's are responsible for the following physiological functions: Increase in the monoaminergic level, Reverse physiological derangements such as improve heart rate variability, decrease platelet activation, decrease expression of inflammatory markers and decrease sympathetic nervous activity at rest and during mental stress tasks. Sigma 1 receptor is a target receptor for SSRI to produce cardio protective action. Mechanism behind this action is described as follows [15]:

ROLE OF SERTRALINE

Patients suffering from chronic heart disease and depressive symptoms show abnormal functioning of hypothalamic pituitary adrenal axis. Due to hyperactivation, cortisol secretion gets altered. Hypersecretion of cortisol further leads to downregulation of endothelial nitric oxide synthase. Sertraline helps in the restoration of hypothalamic pituitary adrenal axis functioning. Endothelial dysfunctioning is strongly associated with cardiovascular events. Sertraline in combination with statins and angiotensin converting enzyme(ACE) inhibitors can protect endothelial dysfunction. Sertraline therefore restore functioning of hypothalamic pituitary adrenal axis, Improve vascular vasodilation via stimulation of calcium mobilization release in the vascular wall and increase production of nitric oxide. A clinical study demonstrated that sertraline exhibit beneficial effect on endothelial functioning and inflammatory status in chronic heart disease patients with depressive symptoms.[16]

ROLE OF DHEA

DHEA dehydroepiandrosterone and its sulphate DHEAS dehydroepiandrosterone sulphate are the steroids secreted from adrenal cortex. The levels of these steroids are expected to decrease with increasing age in both the genders. In postmenopausal women, low amount of DHEA is associated with increase in risk factors for cardiovascular diseases. DHEA shows cardioprotective action, therefore body should have sufficient levels of DHEA. DHEA shows vasoprotective and endothelium protective effects. Molecular mechanism behind cardioprotective role of DHEA still need clarity, but studies shows DHEA is a sigma 1 receptor agonist which is mainly located in the heart and kidney. DHEA shows beneficial effects on cardiovascular system via upregulation of sigma 1 receptor mediated activation of Akt-e NOS signalling pathways.[17]

ROLE OF PAROXETINE

Approximately 20% of the heart patients have depression symptoms. Sympathetic hyperactivity and parasympathetic impairment is the major reasons for depression in acute coronary syndromes. This changes in autonomic nervous systems elevate the heart rate also. In patients suffering from depression there is chronic deficiency of a neurotransmitter i.e. 5-hydroxytryptamine (5-HT) in the spaces between two neurons. This chronic deficiency of 5-HT often leads to the blocking of inhibitory signals of sympathetic nervous system. When

sympathetic inhibitory signals are impaired the activity of sympathetic nervous system is persistently increased. It had been shown that after myocardial infarction, GRK2 expression is increased in the myocardium. RK is a serine/threonine kinase that empowers in phosphorylation of intracellular spaces of initiated G protein coupled receptors. There are 7 GRKs, out of which GRK2 is the most significant as it is associated with heart capacities. Likewise it is profoundly communicated and found in heart. Increment in GRK2 may be because of initiation of beta adrenergic receptors by catecholamines. GRK2 have negative impact on beta adrenergic receptors found in the heart. It causes desensitization of beta adrenergic receptors or downregulation of beta adrenergic receptors articulation in the myocardium. GRK2 contrarily directs nitric oxide synthase movement, glucose digestion, and mitochondrial work, in the myocardium. Proof additionally proposes that GRK2 restraint gives defensive sign by means of a novel sympatholytic pathway, bringing about an improved cardiovascular contractility and obstruction against cardiovascular breakdown movement after MI. SSRI, for example, paroxetine is an intense agonist at sigma 1 receptor that represses GRK2 articulation and encourages in to give cardioprotection[18]

ROLE OF HALOPERIDOL

Haloperidol is a psychotropic prescription drug used in clinical practice for treatment of psychoses like schizophrenia. Inotropic effect of haloperidol was first depicted in neonatal rat refined cardiomyocytes prologue to nanomolar portion of the sigma receptor ligands (+)- 3-PPP ((+)- 3-hydroxyphenyl-N-(1-propyl)piperidine), (+)- pentazocine and haloperidol, incited changes in plentifulness of the cardiomyocytes, comprising of an underlying diminishing, trailed by a transient increment and a last reduction of adequacy. In relative examinations with grown-up rodents separated ventricular myocytes, the extension of sufficiency was much higher in most of the cells. In part of the cells presented to low convergence of sigma receptor ligands, only a decreasing of the contractile response was watched. These trials got proof help of the possibility that the cardiovascular impacts of psychotropic medications utilized are because of official to explicit receptors and not by a cross-talk between the distinctive receptor frameworks. In all the previously mentioned tests changes of the reaction to sigma ligands was available. [19]

ROLE OF PRE034

Recent studies have suggested that σ_1 R agonists have potent cardioprotective effects in mice. Intracerebroventricular infusion of the σ_1 R agonist PRE-084 for 1 month improved both

mental and cardiac functioning in mice in which MI was induced. PRE-084 protected the heart by reducing myocardial I/R injury in rats, as proved by preserved cardiac function and reduced myocardial apoptosis. This occurs via changing the expression of apoptosis-related proteins (Bcl-2 and Bax) after activating the Akt-eNOS pathway. Apoptosis is the major pathogenic mechanism of myocardial I/R injury. Since myocardial cells are nonregenerative, apoptosis may cause myocardial dysfunction, which surfaces during ischemia and then is aggravated after reperfusion. Myocardial apoptosis is increased after IR injury, and PRE-084 reduced its extent. PRE-084 upregulated the expression of Bcl-2 protein while downregulating the expression of Bax and caspase-3 proteins, thereby increasing the ratio of Bcl-2 to Bax. This suggest that PRE-084 may decrease IR-induced apoptosis of myocardial cells by upregulating Bcl-2 expression and downregulating Bax and caspase-3 expression. Studies have shown that some signaling molecules have the function of upstream apoptotic regulation during myocardial reperfusion injury. PRE-084 treatment significantly increases the expression of p-Akt and p-eNOS, suggesting that PRE-084 protects the heart by activating the Akt-eNOS pathway. PRE-084 can protect the heart by stimulating the σ 1R in brain, which may also contribute to a certain extent to the cardioprotective effects. Finally, σ 1R interactions with ion channels, including Calcium, potassium, sodium and chloride channels. These molecular mechanisms may also contribute to its myocardial protective effects. In conclusion, it can be said that PRE-084 reduces apoptosis and improves cardiac function following reperfusion via activation of the Akt-eNOS signaling pathway[20]

CONCLUSION

Cardiovascular system disorders especially hypertension belong to the most common causes of morbidity and mortality in the developed countries with an enormous impact on the population and economics. Stimulation of sigma receptor with ligand binding in the cardioprotection activity is the novel concept yet to be discovered. However various animal model studies have proved the cardioprotective activity of sigma receptor ligands such as Fisetin, ANAVEX2-73, Ketamine and PRE-034. Selective serotonin reuptake inhibitors target the sigma receptors to produce cardioprotective effects. Various SSRIs such as fluvoxamine, DHEA, sertraline and paroxetine show cardioprotective activity via targeting sigma receptors. Therefore, it can be concluded that sigma receptor ligands helps to improves the therapeutic agents.

REFERENCES:

- [1] Shu-Zhong Jiang, Wen Lu, Xue-Feng Zong, Hong-Yun Ruan, & Yi Liu.. Obesity and hypertension (Review). *Experimental and Therapeutic Medicine*, vol ED-12(4), pp. 2395-2399, 2016.
- [2] Thomas D. Giles MD, Barry J. Materson MD, Jay N. Cohn MD, & John B. Kostis MD. Definition and classification of Hypertension: An Update. *The international journal of hypertension*, vol ED-11(11), pp. 611-614, 2009..
- [3] Li, Changwei, Kelly, Tanika N.. Hypertension in India. *The international journal of hypertension*, vol ED- 32(6), 1189-1191, 2014.
- [4] P Foex, John W Swear. (2004). Hypertension: Pathophysiology and treatment. *Continuing education in anaesthesia critical care and pain*, vol ED -4, pp. 71-75. 2004.
- [5] F.M. Tedla, A. Brar, R. Browne, C. Brown. (2011). Hypertension in chronic kidney disease: Navigating the Evidence. *International Journal of Hypertension*, vol ED-9, 2011.
- [6] A. Virdis, C. Giannarelli, M. Fritsch, S. Taddei, L. Ghiadoni. (2010). Cigarette smoking and hypertension. *Current pharmaceutical design*, vol ED-16, 2010,
- [7] Arun Chockalingam, Norman R Campbell, J George Fodor.. Worldwide epidemic of hypertension. *The Canadian journal of cardiology*, vol ED -22(7), pp. 553-555, 2006.
- [8] Giuliano Pinna, Claudio Pascale, Micaela La Ragina, Francesco Orlandini. (2012) Hypertension in the elderly. *Italian Journal of Medicine*, vol ED 6(4), pp. 285-294, 2012.
- [9] Gareth Beevers, Gregory Y H Lip, Eoin O'Brien.. The pathophysiology of hypertension. *BMJ*, vol ED -322(7291), pp. 912-916, 2001.
- [10] Cobos, E.J., Entrena, J.M., Nieto, F.R., Cendan, C.M., and Pozo, E. Del. (2008). Pharmacology and therapeutic potential of sigma(1) receptor ligands. *Curr Neuropharmacol*, vol ED -6, pp. 344-366, 2008.
- [11] Rae R Matsumoto.. Targeting sigma receptors: novel medication development for drug abuse and addiction, *Expert Rev Clin Pharmacol*, vol ED -2(4), pp. 351-358, 2009.

- [12] T. Hayashi* and T.-P. Su. The Sigma Receptor: Evolution of the Concept in Neuropsychopharmacology. *Current Neuropharmacology*, vol ED -3, pp. 267-280, 2005.
- [13] Bih-Cheng Chen, Kalaiselvi Sivalingam, Marthandam Asokan Shibu, Rajendran Peramaiyan, Cecilia Hsuan Day, Chia-Yao Shen, Chao-Hung Lai, Ray-Jade Chen, Vijaya Padma Viswanadha, Ya-Feng Chen, Chih-Yang Huang. (2018). Protective Effect of Fisetin Against angiotensin II-induced Apoptosis by Activation of IGF-IR-PI3K-Akt Signaling in H9c2 cells and Spontaneous hypertension rats. *Phytomedicine*,.
- [14] Mikhail V. Voronin & Ilya A. Kadnikov.. Contribution of Sigma-1 receptor to cytoprotective effect of afobazol. *Pharmacology Research & Perspectives*, vol ED -4, pp. 273.
- [15] Md. Shenuarin Bhuiyan, Hideaki Tagashira, and Kohji Fukunaga.. Crucial Interactions Between Selective Serotonin Uptake Inhibitors and Sigma-1 Receptor in Heart Failure. *Journal of Pharmacological Sciences*, vol ED -121, pp. 177-184, 2012.
- [16] C Pizzi, S Mancini, L. Angeloni, F Fontana, L Manzoli & GM Costa. Effects of Selective Serotonin Reuptake Inhibitor Therapy on Endothelial Function and Inflammatory Markers in Patients With Coronary Heart Disease. *Clinical Pharmacology And Therapeutics*, vol ED -86(6), pp. 527-532, 2009.
- [17] Md. Shenuarin Bhuiyan and Kohji Fukunaga. Stimulation of Sigma-1 receptor signalling by dehydroepiandrosterone ameliorates pressure overload-induced hypertrophy and dysfunctions in ovariectomized rats. *Expert Opin. Ther. Targets*, vol ED -13(11), pp. 1253-1265, 2009.
- [18] Xiuqing Tian, Qing Wang, Rui Guo, et al. Effects of paroxetine-mediated inhibition of GRK 2 expression on depression and cardiovascular function in patients with myocardial infarction. *Neuropsychiatric Disease and Treatment*, vol ED -12, pp. 2333-2341, 2016.
- [19] M. Novakova.. Effect of Sigma Receptor Ligand Haloperidol in Guinea Pig Heart. *Acta Vet. Brno*, vol ED -73, pp. 313-320, 2014..
- [20] Qi-Jun Gao, Bo Yang¹, Jing Chen¹, Shao-Bo Shi¹, Hong-Jie Yang¹, Xin Liu.. Sigma-1 Receptor Stimulation with PRE-084 Ameliorates Myocardial Ischemia-Reperfusion Injury in Rats. *Chinese Medical Journal*, vol ED -131(5), pp. 539-543, 2018