Nat. Volatiles & Essent. Oils, 2022; 9(2): 721-734

NVEO
Natural Volatiles &
Essential Oils

Cardiovascular And Neurologic Applications Of Biomarkers

[1]Akash Limba Kawale , [2]Nirmal Joshi , [3]Kaushal B. Navadiya , [4]Ayesha Nisar Shaikh* , [5]Utkarsh Trivedi , [6]Ayushmann Roy

[1]Dept. of Pharmacy, Godavari Institute of Pharmacy, Kolpa, Latur.

[2]Asst. Professor, (PhD Scholar), Amrapali Institute of Pharmacy and Sciences, Shiksha Nagar, Lamachaur, Haldwani, Nainital, Uttarakhand.

[3]Dept. of Pharmacy, C.K. Pithwalla Institute of Pharmaceutical Science and Research, Surat, Gujarat

[4]Department of Pharmaceutics, JMCT Institute of Pharmacy, Wadala road, Nashik, Maharashtra

[5]Department of Pharmacy, Uttaranchal Institute of Pharmaceutical Sciences, Dehradun, Uttarakhand

[6]Rungta College of Pharmaceutical Sciences & Research, Kohka Kurud Bhilai.

Abstract

Biomarkers are inexpensive, repeatable, and accessible diagnostic tools. Recent research has focused on their well-known benefits. Cardiovascular and neurological illnesses share risk factors and pathogenic pathways, affecting biomarker use and interpretation. Neurological illnesses affect hs-TroponinT, CK-MB, and NTproBNP. Galectin-3, lysophosphatidylcholine, copeptin, sST2, S100B, myeloperoxidase, and GDF-15 have been studied as cardiovascular and neurology alternatives. Due to their limited specificity, values require clinical judgement and additional tests.

Keywords: Biomarkers, Natriuretic Peptides, apoptosis, Creatine Kinase

Introduction

Biomarkers indicate organ and system health. Proteins, enzymes, and hormones have fluctuating concentrations in normal and pathological circumstances. They're useful in a range of heart disease cases, and more research is underway. Biomarker research began in 1954 when enzymes were used to diagnose myocardial infarction [1]. Since then, they've been employed to treat heart failure and ischemia. Cardiovascular disease and neurological pathology share numerous risk variables, which can alter biomarker values and interpretations, leading to medical judgement errors. Considering this, we compared and assessed all recent biomarkers.

History of Cardiac Biomarker

First AMI biomarker: AST [6]. AST was common in the 1960s [7]. AST isn't unique to cardiac muscle, hence its identification isn't specific for injury. 1970s saw the introduction of LDH and CK (CK). CK is

more specific than LDH in AMI patients with muscle or liver dysfunction [8]. Myoglobin distributes heart oxygen to striated muscle. First myoglobin test: 1978. Myoglobin rises after myocardial injury and can detect AMI [10]. Myoglobin testing no longer indicates myocardial necrosis in the era of hs-cTn [11, 12]. Electrophoresis identified CK-MB and LDH 1+2 [13]. Cardiac muscle has 25–30% CK-MB vs. 1% CK-MM. WHO employed these tests in 1979 [14] to rule out AMI. Inaccuracy and false-positives invalidated these tests. Finding a cardiac biomarker.

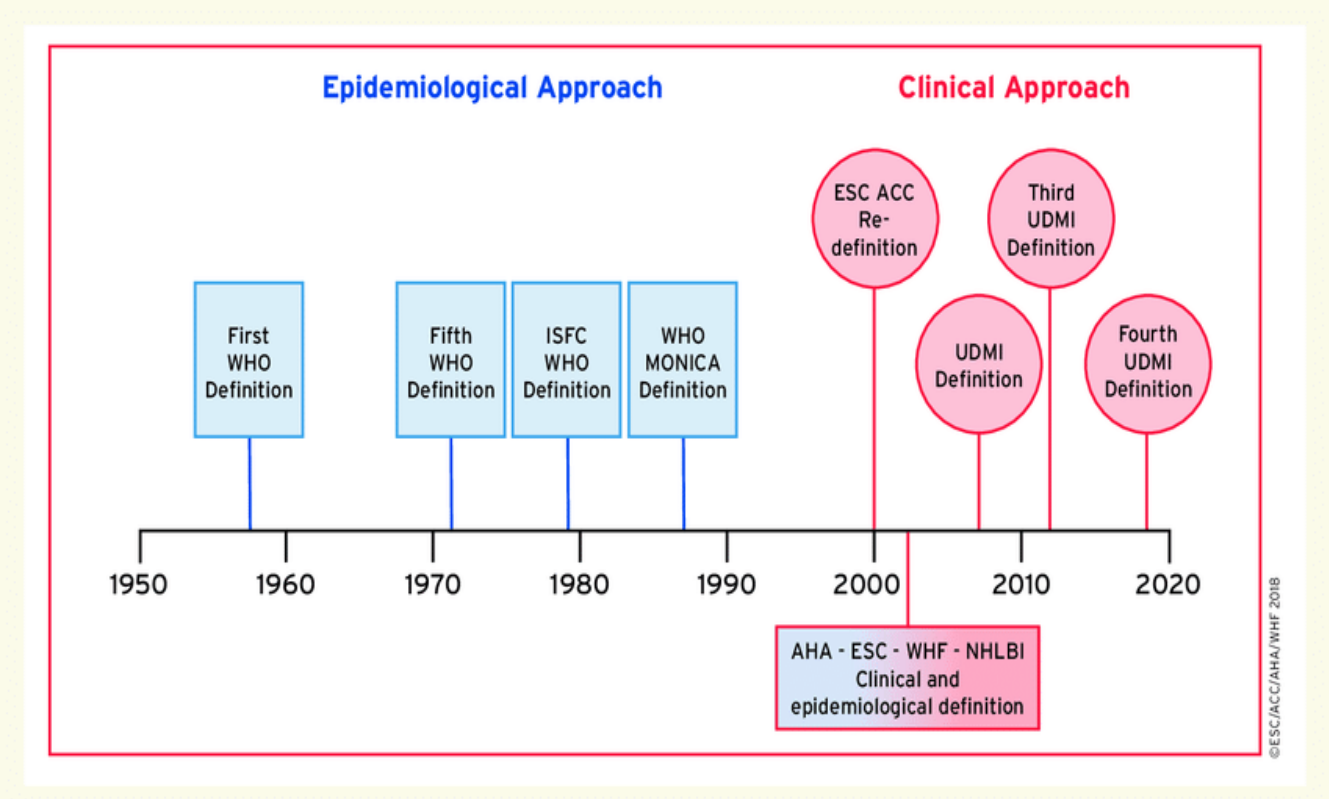

Fig: 1 A timeline of the development of cardiac biomarkers for the diagnosis of acute myocardial infarction

Biomarkers

Natriuretic Peptides

NPS regulates blood pressure and extracellular fluid volume. Atrial and b-type natriuretic peptides (ANP and BNP) are hormones generated by cardiomyocytes in response to mechanical stimuli. They cause diuresis, natriuresis, and vasodilation. Urodilatin is a kidney-produced ANP isoform with four N-terminal residues. C-type natriuretic peptide (CNP) is largely generated by the endothelium and released in response to numerous stimuli (e.g., increased shear stress and cytokine signalling) to exert vasodilatory and anti-proliferative effects in the vasculature. CNP is only mildly raised in HF and not a direct therapeutic target.

Synthesis and Secretion of Natriuretic Peptides

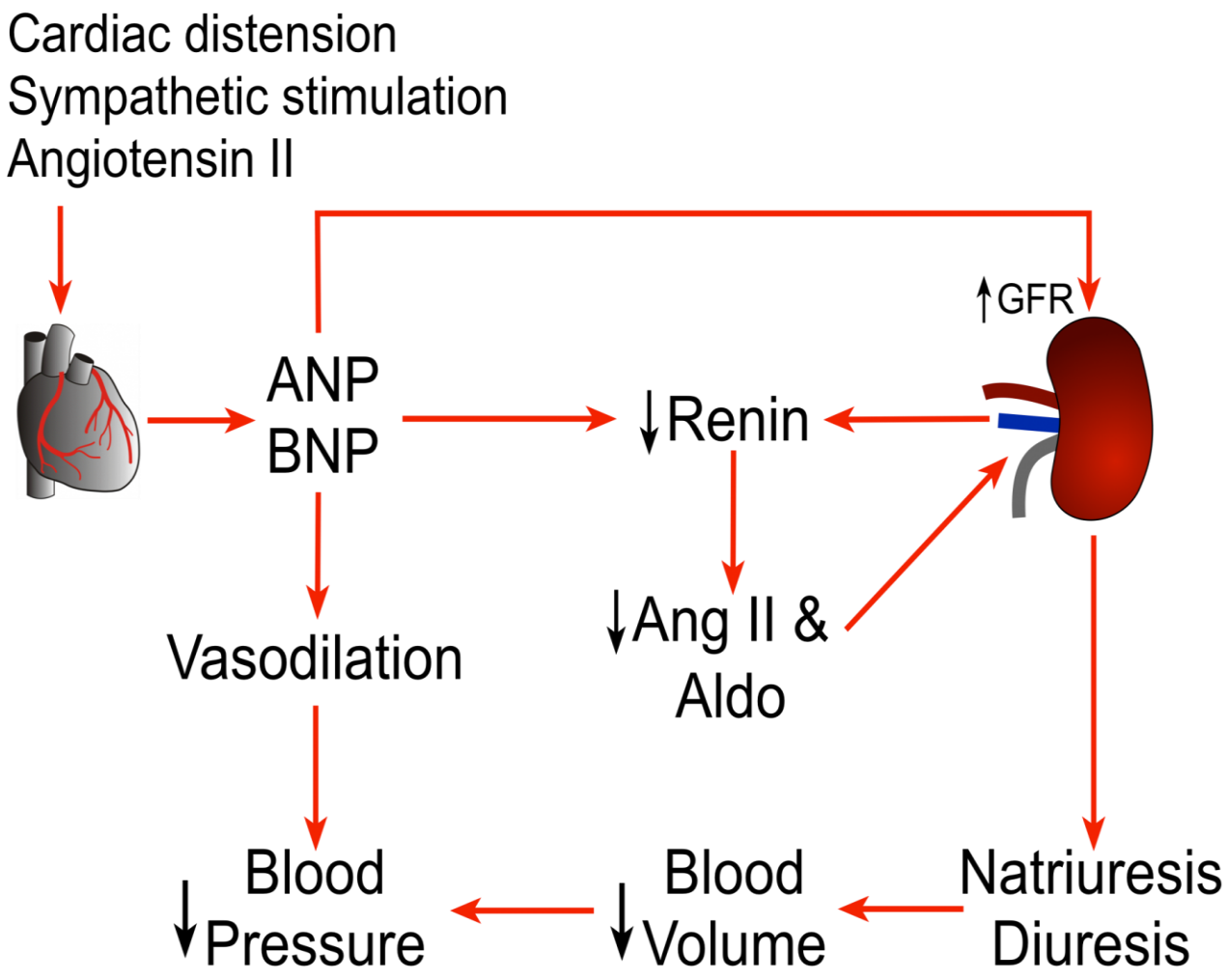

Fig: 2 Synthesis and Secretion of Natriuretic Peptides

NPPA and NPPB on 1p36.22 encode atrial and b-type natriuretic peptides. During development and sickness, epigenetic regulators and transcription factors coordinate locus control. Atrial cardiomyocytes express NPPA but cardiac NPPB is low. Mechanical and neurohormonal stimulation modify the locus' chromatin environment, activating both atrial and ventricular genes. Numerous HF traits, including hemodynamic stress and increased wall stretch, activate the NPPA/NPPB locus in atrial and ventricular tissue. Mitogen-activated protein kinases (MAPKs), specifically ERK-signaling, drive HF-related NPPA/NPPB gene expression. GATA4, NFAT, and Myocardin are key transcription factors.

NPPA and NPPB mRNA translation yields 151- and 134-amino acid preprohormones that are enzymatically transformed into proANP and proBNP. Furin makes intracellular BNP, while Corin cleaves proANP to make ANP. In healthy settings, ProANP and processed BNP are released concurrently from atrial granules. Pressure overload and wall stress generate ANP and BNP elevations in HF patients.

Globally, troponins COPD kills. COPD is a lung multimorbidity, with CVD being the most frequent [1]. Cardiovascular diseases worsen COPD patients' quality of life, healthcare costs, and death [2, 3]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends utilising a CVD risk calculator for COPD [4]. Pathophysiological connections between COPD and CVD remain unclear [5]. Smoking, inactivity, and metabolic syndrome cause COPD [6]. COPD variables can exacerbate CVD and COPD coexistence. Both illnesses cause systemic inflammation, hypoxemia, sleep disturbances, exacerbations, and lung hyperinflation.

Muscle and heart contain troponins. Troponins T and I are MI biomarkers. cTn screens patients for cardiac risk. Troponin thresholds are lower than for MI [7, 8].

Cardiac Troponins Metabolism

During apoptosis, caspase enzymes and intracellular proteinases increase in activity, cleaving DNA and protein structures while preserving cell membrane integrity [46]. Modern apoptosis detection methods include electron microscopy, immunohistochemistry, flow cytofluorimetry, and TUNEL (Terminal deoxynucleotide Transferase—mediated dUTP—biotin Nick—End Labeling) [47,48,49]. TUNEL study verifies apoptosis' major cause, caspase-induced DNA degradation. The approach works by specifically attaching terminal deoxynucleotidyl transferase to damaged DNA strands [49].

Weil et al. (2017) used balloon occlusion to simulate short-term (10-min) ischemia in pigs. Angiography verified occlusion. After reperfusion, several animals' myocardium was taken for histological analysis. In another experiment on (live) animals, troponin I was measured after reperfusion using a reasonably sensitive method (Life Diagnostics, West Chester, Pennsylvania) in regional (anterior interventricular vein) and systemic (jugular) blood serum samples. Histological tests showed no ischemia damage or necrosis. Short-term ischemia caused a sixfold increase in TUNEL-positive cardiomyocytes compared to the control area. After 10 min, troponin I levels rose modestly. After 30 min, they reached the 99th percentile (38 ng/L) and peaked at 24 h (1021 574 ng/L). Regional and systemic troponin I levels correlated well. Short-term ischemia does not cause cardiomyonecrosis but causes cardiomyocyte death and troponin release [50]. This study is confined to 24 h, therefore it's unknown what would happen next with troponins and cardiomyocytes. In real practise, early identification of troponins by moderately sensitive techniques is difficult/impossible due to wash-out, unlike in the experiment described above.

Cardiomyocyte apoptosis can occur without myocardial ischemia. Myocardial distension increases programmed cell death, according to Cheng et al. In this situation, stretching of the myocardium can occur in physiological and pathological settings (such as heart failure and arterial hypertension), possibly contributing to an increase in troponins [52,53,54]. Singh et al. (2001) studied the effect of increased neurohumoral stimulation on apoptosis and discovered that beta1-adrenergic receptor stimulation induces apoptosis via activation of adenylyl cyclase [55], while beta2-adrenergic receptor stimulation is antiapoptotic [56,57]. With age, beta2-adrenergic receptor density decreases [58]. Thus, apoptosis may have a role in troponin increase in cardiac failure, age, and prolonged/excessive exercise. An rise in troponins in these individuals can lead to overdiagnosis of AMI, especially when employing sensitive test systems and when doctors depend solely on laboratory data. Manjunath et al. (2018) confirms this. A

young patient with chest pain was admitted to the ER with elevated troponin I (0.123 ng/mL vs. 0.055 ng/mL). Unfavorable family history and hypercholesterolemia led doctors to suspect myocardial infarction. ECG, Echo-CG, and coronary angiography showed no myocardial ischemia. The young man was active in athletics and ran many miles the day before admission to prepare for a marathon [59].

In pigs, increasing left ventricular preload causes apoptosis and troponin I release without ischemia. Animals got 300 g/min phenylephrine for 1 h to raise end-diastolic pressure. The baseline release of troponin I (16 20 ng/L) was modest, but 30 min after the increase in end-diastolic pressure, it was above the 99th percentile. After 1 h, it was 856 956 ng/L (p = 0.01) and remained elevated after 24 h (1462 1691 ng/L). Pathological investigation demonstrated apoptosis of cardiac cells (31.3 11.9 vs. 4.6 3.7; p 0.01), which reverted to normal after 24 h (6.2 5.6 myocytes/cm2; p = 0.46) without necrosis [60]. Thus, apoptosis, not cardiomyocyte destruction, increased cardiac troponins.

Creatine Kinase

LCK is inactivated by proteolysis. CK clearance isn't influenced by impaired liver or renal function or urine. Hypothyroidism lowers CK clearance. Increased B subunit synthesis in damaged skeletal muscle, as during foetal development, can raise CK-MB without AMI. phylogeny [8] [9]

Rhabdomyolysis, exercise, and trauma elevate CK-MB. Skeletal muscles have less CK-MB. Autoimmune and inflammatory myopathies can raise CK-MB levels. [10] AMI should be suspected in patients with quickly rising and dropping CK-MB. CK-MB was used to identify acute MI in the 1980s and 1990s, however its specificity was limited. Better measurements increase CK-specificity MBs. Immunoenzymometric tests employing M and B subunit-specific antibodies are selective and sensitive. [15] Cross-reactive alkaline phosphatase in plasma raises monoclonal antibody testing for CK-MB. Patients with ALS or progressive spinal muscular atrophy may have elevated CK values. Astrocytes and oligodendrocytes express CK more than neurons. Neuropathies and radiculopathies elevate CK. Neuropathies are caused by damaged motor neuron axons. Axonal degeneration raised CK in 27% of CIDP patients. CK is affected by Guillain-motor Barre's paralysis. Muscle axonal loss affects membrane integrity. CMT elevates CK [58,59].

Biomarker for central neuropathology. CK diagnoses tonic-clonic seizures in EDs. Nonepileptic psychogenic seizures and vasovagal syncope had decreased CK [60]. Meningitis raises CK-BB.

Creatine protected neurons from harmful metabolites, glucose deprivation, and serum. CK regulates brain cell energy [64,65]. In Alzheimer's dementia, reactive oxygen and nitrogen species inactivate CK, reducing overall CK activity (BB-CK activity fell 86 percent and CK expression fell 14 percent [66]). Epilepsy, schizophrenia, and maniac-depressive psychosis have low CK. Huntington's and Pick diseases cause fatigue [69,70]. Huntington's disease causes neuronal dysfunction by downregulating CK-MB. Creatine may be replaced by CK-MB [71]. Children with benign paroxysmal vertigo had higher CK-MB levels, suggesting a pathophysiological link.

Lysophosphatidylcholine

LPC dominates oxidised LDL. 100M Health LPC [2]. LPC levels are disease-related. Atherosclerosis, inflammation, diabetes, adrenoleukodystrophy, and squamous cervical cancer have higher LPC levels than infectious illnesses, ovarian cancer, and colorectal cancer. LPC promotes growth, inflammation, and oxidative stress. Our research reveals how LPC causes disease. GPL are macrophospholipids. GPLs have esterified glycerol backbones. Third hydroxyl phosphorylated. Phosphoric acid results (PA). Choline or ethanolamine esters generate PC and PE. Most prevalent mammalian membrane GPL

Most in vivo PLs have a saturated fatty acyl residue in sn-1 and an unsaturated one in sn-2 (e.g., arachidonic or docosahexaenoic acid, which contain four or six double bonds, respectively). LPLs are made by phospholipases. Arachidonic acid (C20:4) is vulnerable to oxidation, and its metabolites are biologically active.

Growth differentiation factor-15

GDF-15 is a cytokine produced in cardiomyocytes, adipocytes, macrophages, endothelial cells, and smooth vascular musculature during tissue injury, inflammation, and mechanical or oxidative stress. Increased levels indicate healing of lesions. Heart failure, hypertrophy, atherosclerosis, endothelial dysfunction, and recurrent myocardial infarction are linked to GDF-15. After a myocardial infarction, GDF-15 levels rise quickly and remain high for days. AMI patients have higher scores than individuals with unstable angina or non-cardiac chest pain. GDF-15 boosts the prognostic value of the GRACE (Global Registry of Acute Coronary Events) score in patients with NSTEMI myocardial infarction, even more than NT-proBNP [166]. GDF-15 improves the HAS-BLED risk score, which is strongly correlated with bleeding risk [169]. GDF-15 levels predict all-cause death in non-ischemic individuals. This biomarker rises as heart failure progresses and could help asymptomatic patients [68].

GDF-15, released by maturing erythroblasts, regulates hepcidin and iron homeostasis. Ineffective erythropoiesis (thalassemia or sickle cell) and inflammation, acute injury, cancer, and chronic kidney disease modify blood GDF-15 concentrations [90].

This biomarker isn't well-studied in neurological pathology. It may help stroke sufferers, though. GDF-15 stimulates angiogenesis under ischemic conditions, which may explain elevated levels in ischemic stroke patients [73]. In patients who had thrombolysis or thrombectomy, higher GDF-15 levels on entry increased 3-month mortality. After a stroke, values decline within 24 h but can sometimes last 7 days. GDF-14 levels correspond to the NIHSS score, with a higher level indicating a more severe ischemia injury [74]. GDF-15 predicts a first ischemic stroke in hypertensive individuals [74].

Conclusion

Most cardiovascular biomarkers were effective in neurological disorders. This narrative literature study showed how to differentiate between the two diseases (cardiac and neurologic). As it's challenging to find a biomarker with perfect specificity and sensitivity for a particular pathology, clinical context and

additional studies are usually helpful for a good diagnosis. Biomarkers can be particularly useful in determining prognosis, especially in cardiac and neurological disorders, as they often interact. Better and more specific biomarkers require more investigation. This review and prior studies focus on LPC. This is partly due to the LPL's sensitivity. Low-resolution mass spectrometers accomplish this. LPC is a stable chemical that doesn't react with other compounds, which aids in its determination. It's unclear if and which LPL are good biomarkers of (inflammatory) disorders. Contradictory LPC effects in experimental models and patient samples may be related to saturation and/or chain length.

References

1. Ladue J.S., Wroblewski F., Karmen A. Serum glutamic oxaloacetic transaminase activity in human acute transmural myocardial infarction. Science. 1954; 120: 497– 499. doi: 10.1126/ science.120.3117.497
2. Goetze J.P., Friis-Hansen L., Rehfeld J.F., Nilsson B., Svendsen J.H. Atrial secretion of B-type natriuretic peptide. Eur. Hear. J. 2006;27:1648–1650. doi: 10.1093/eurheartj/ehl109.
3. Brown, D., Nakagome, K., Cordes, J., Brenner, R., Grunder, G., Keefe, R. S. E., et al. (2019). Evaluation of the efficacy, safety, and tolerability of BI 409306, a novel phosphodiesterase 9 inhibitor, in cognitive impairment in schizophrenia: a randomized, double-blind, placebo-controlled, phase II trial. Schizophr. Bull. 45, 350–359. doi: 10.1093/schbul/sby049
4. Bueno, O. F., De Windt, L. J., Tymitz, K. M., Witt, S. A., Kimball, T. R., Klevitsky, R., et al. (2000). The MEK1-ERK1/2 signaling pathway promotes compensated cardiac hypertrophy in transgenic mice. EMBO J. 19, 6341–6350. doi: 10.1093/emboj/19.23.6341
5. Mukesh Kr. Singh, Ajay Kumar, Roshan Kumar, P. Satheesh Kumar, P. Selvakumar, & Anurag Chourasia. (2022). Effects of Repeated Deep Frying on Refractive Index and Peroxide Value of Selected Vegetable Oils. International Journal for Research in Applied Sciences and Biotechnology, 9(3), 28–31. https://doi.org/10.31033/ijrasb.9.3.6
6. Cargill, R. I., Barr, C. S., Coutie, W. J., Struthers, A. D., and Lipworth, B. J. (1994). C-type natriuretic peptide levels in cor pulmonale and in congestive heart failure. Thorax 49, 1247–1249. doi: 10.1136/thx.49.12.1247
7. Carvajal, J. A., Germain, A. M., Huidobro-Toro, J. P., and Weiner, C. P. (2000). Molecular mechanism of cGMP-mediated smooth muscle relaxation. J. Cell. Physiol. 184, 409–420. doi: 10.1002/1097-4652(200009)184:3<409::AID-JCP16>3.0.CO;2-K
8. Cataliotti, A., Tonne, J. M., Bellavia, D., Martin, F. L., Oehler, E. A., Harders, G. E., et al. (2011). Long-term cardiac pro-B-type natriuretic peptide gene delivery prevents the development of hypertensive heart disease in spontaneously hypertensive rats. Circulation 123, 1297–1305. doi: 10.1161/CIRCULATIONAHA.110.981720
9. Catuogno, S., Di Martino, M. T., Nuzzo, S., Esposito, C. L., Tassone, P., and de Franciscis, V. (2019). An anti-BCMA RNA aptamer for miRNA intracellular delivery. Mol. Ther. Nucleic Acids 18, 981–990. doi: 10.1016/j.omtn.2019.10.021
10. Celik, S., Sadegh, M. K., Morley, M., Roselli, C., Ellinor, P. T., Cappola, T., et al. (2019b). Antisense regulation of atrial natriuretic peptide expression. JCI Insight 4:e130978. doi: 10.1172/jci.insight.130978

11. Celik, S., Karbalaei-Sadegh, M., Radegran, G., Smith, J. G., and Gidlof, O. (2019a). Functional screening identifies MicroRNA regulators of corin activity and atrial natriuretic peptide biogenesis. Mol. Cell. Biol. 39:e00271-19. doi: 10.1128/MCB.00271-19
12. Charles, C. J., Espiner, E. A., Nicholls, M. G., Richards, A. M., Yandle, T. G., Protter, A., et al. (1996). Clearance receptors and endopeptidase 24.11: equal role in natriuretic peptide metabolism in conscious sheep. Am. J. Physiol. 271, R373–R380. doi: 10.1152/ajpregu.1996.271.2.R373
13. Awuchi, C. G., Amagwula, I. O., Priya, P., Kumar, R., Yezdani, U., & Khan, M. G. (2020). Aflatoxins in foods and feeds: A review on health implications, detection, and control. Bull. Environ. Pharmacol. Life Sci, 9, 149-155.
14. Chen, H. H., Neutel, J. M., Smith, D. H., Heublein, D. M., and Burnett, J. C. (2016). ZD100 a novel particulate-guanylyl-cyclase a receptor activator in human resistant "like" hypertension – a first in human study. J. Card. Fail. 22:S33. doi: 10.1016/j.cardfail.2016.06.103
15. Chen, S., Sen, S., Young, D., Wang, W., Moravec, C. S., and Wu, Q. (2010). Protease corin expression and activity in failing hearts. Am. J. Physiol. Heart Circ. Physiol. 299, H1687–H1692. doi: 10.1152/ajpheart.00399.2010
16. Kumar, R., Saha, P., Kumar, Y., Sahana, S., Dubey, A., & Prakash, O. (2020). A REVIEW ON DIABETES MELLITUS: TYPE1 & TYPE2
17. . Integr. Comp. Physiol. 318, R669–R676. doi: 10.1152/ajpregu.00354.2019
18. Cleland, J. G., and Swedberg, K. (1998). Lack of efficacy of neutral endopeptidase inhibitor ecadotril in heart failure. The International Ecadotril Multi-centre Dose-ranging Study Investigators. Lancet 351, 1657–1658. doi: 10.1016/S0140-6736(05)77712-6
19. Cohen, D., Koh, G. Y., Nikonova, L. N., Porter, J. G., and Maack, T. (1996). Molecular determinants of the clearance function of type C receptors of natriuretic peptides. J. Biol. Chem. 271, 9863–9869. doi: 10.1074/jbc.271.16.9863
20. Crozier, I. G., Nicholls, M. G., Ikram, H., Espiner, E. A., Gomez, H. J., and Warner, N. J. (1986). Haemodynamic effects of atrial peptide infusion in heart failure. Lancet 2, 1242–1245. doi: 10.1016/S0140-6736(86)92675-9
21. KUMAR, R., SAHA, P., SARKAR, S., RAWAT, N., & PRAKASH, A. (2021). A REVIEW ON NOVEL DRUG DELIVERY SYSTEM. IJRAR-International Journal of Research and Analytical Reviews (IJRAR), 8(1), 183-199.
22. Del Ry, S., Passino, C., Maltinti, M., Emdin, M., and Giannessi, D. (2005). C-type natriuretic peptide plasma levels increase in patients with chronic heart failure as a function of clinical severity. Eur. J. Heart Fail. 7, 1145–1148. doi: 10.1016/j.ejheart.2004.12.009
23. Raj, A., Tyagi, S., Kumar, R., Dubey, A., & Hourasia, A. C. (2021). Effect of isoproterenol and thyroxine in herbal drug used as cardiac hypertrophy. Journal of Cardiovascular Disease Research, 204-217.
24. Dickey, D. M., Yoder, A. R., and Potter, L. R. (2009). A familial mutation renders atrial natriuretic Peptide resistant to proteolytic degradation. J. Biol. Chem. 284, 19196–19202. doi: 10.1074/jbc.M109.010777
25. Dickstein, K., De Voogd, H. J., Miric, M. P., Willenbrock, R., Mitrovic, V., Pacher, R., et al. (2004). Effect of single doses of SLV306, an inhibitor of both neutral endopeptidase and endothelin-converting enzyme, on pulmonary pressures in congestive heart failure. Am. J. Cardiol. 94, 237–239. doi: 10.1016/j.amjcard.2004.03.074

26. Dong, N., Chen, S., Yang, J., He, L., Liu, P., Zheng, D., et al. (2010). Plasma soluble corin in patients with heart failure. Circ. Heart Fail. 3, 207–211. doi: 10.1161/CIRCHEARTFAILURE.109.903849
27. Duan, Q., McMahon, S., Anand, P., Shah, H., Thomas, S., Salunga, H. T., et al. (2017). BET bromodomain inhibition suppresses innate inflammatory and profibrotic transcriptional networks in heart failure. Sci. Transl. Med. 9:eaah5084. doi: 10.1126/scitranslmed.aah5084
28. Elsner, D., Muders, F., Muntze, A., Kromer, E. P., Forssmann, W. G., and Riegger, G. A. (1995). Efficacy of prolonged infusion of urodilatin [ANP-(95-126)] in patients with congestive heart failure. Am. Heart J. 129, 766–773. doi: 10.1016/0002-8703(95)90328-3
29. Emoto, N., Raharjo, S. B., Isaka, D., Masuda, S., Adiarto, S., Jeng, A. Y., et al. (2005). Dual ECE/NEP inhibition on cardiac and neurohumoral function during the transition from hypertrophy to heart failure in rats. Hypertension 45, 1145–1152. doi: 10.1161/01.HYP.0000168944.29525.da
30. Faghihi, M. A., Modarresi, F., Khalil, A. M., Wood, D. E., Sahagan, B. G., Morgan, T. E., et al. (2008). Expression of a noncoding RNA is elevated in Alzheimer's disease and drives rapid feed-forward regulation of beta-secretase. Nat. Med. 14, 723–730. doi: 10.1038/nm1784
31. Feldman, A. M., Ray, P. E., Silan, C. M., Mercer, J. A., Minobe, W., and Bristow, M. R. (1991). Selective gene expression in failing human heart. Quantification of steady-state levels of messenger RNA in endomyocardial biopsies using the polymerase chain reaction. Circulation 83, 1866–1872. doi: 10.1161/01.CIR.83.6.1866
32. Nyarko, R. O., Prakash, A., Kumar, N., Saha, P., & Kumar, R. (2021). Tuberculosis a globalized disease. Asian Journal of Pharmaceutical Research and Development, 9(1), 198-201.
33. Fujisaki, H., Ito, H., Hirata, Y., Tanaka, M., Hata, M., Lin, M., et al. (1995). Natriuretic peptides inhibit angiotensin II-induced proliferation of rat cardiac fibroblasts by blocking endothelin-1 gene expression. J. Clin. Invest. 96, 1059–1065. doi: 10.1172/JCI118092
34. Gafford, J. T., Skidgel, R. A., Erdos, E. G., and Hersh, L. B. (1983). Human kidney "enkephalinase", a neutral metalloendopeptidase that cleaves active peptides. Biochemistry 22, 3265–3271. doi: 10.1021/bi00282a035
35. Galo, J., Celli, D., and Colombo, R. (2020). Effect of sacubitril/valsartan on neurocognitive function: current status and future directions. Am. J. Cardiovasc. Drugs 21, 267–270. doi: 10.1007/s40256-020-00445-7
36. Kumar, R., & Dubey, A. PHYTOCHEMICAL INVESTICATION AND HEPTOPROTECTIVE EVALUTION ACACIA RUBICA EXTRACT ISONIZED AND PARACETAMOL INDUSED ANIMAL TOXICITY. Turkish Journal of Physiotherapy and Rehabilitation, 32, 3.
37. Giannessi, D., Del Ry, S., and Vitale, R. L. (2001). The role of endothelins and their receptors in heart failure. Pharmacol. Res. 43, 111–126. doi: 10.1006/phrs.2000.0758
38. Kumar, R., & Dubey, A. PHYTOCHEMICAL INVESTICATION AND HEPTOPROTECTIVE EVALUTION ACACIA RUBICA EXTRACT ISONIZED AND PARACETAMOL INDUSED ANIMAL TOXICITY. Turkish Journal of Physiotherapy and Rehabilitation, 32, 3.
39. Sahana, S., Kumar, R., Nag, S., Paul, R., Chatterjee, I., & Guha, N. (2020). A REVIEW ON ALZHEIMER DISEASE AND FUTURE PROSPECTS.
40. Gomes, C. P. C., Schroen, B., Kuster, G. M., Robinson, E. L., Ford, K. I, Squire, B., et al. (2020). Regulatory RNAs in heart failure. Circulation 141, 313–328. doi: 10.1161/CIRCULATIONAHA.119.042474

41. Gori, M., D'Elia, E., Iorio, A., Iacovoni, A., and Senni, M. (2020). Clinical application of personalized medicine: heart failure with preserved left ventricular ejection fraction. Eur. Heart J. Suppl. 22, L124–L128. doi: 10.1093/eurheartj/suaa151
42. Saha, P., Kumar, R., Nyarko, R. O., Kahwa, I., & Owusu, P. (2021). HERBAL SECONDARY METABOLITE FOR GASTRO-PROTECTIVE ULCER ACTIVITY WITH API STRUCTURES.
43. Greenberg, B., Butler, J., Felker, G. M., Ponikowski, P., Voors, A. A., Desai, A. S., et al. (2016). Calcium upregulation by percutaneous administration of gene therapy in patients with cardiac disease (CUPID 2): a randomised, multinational, double-blind, placebo-controlled, phase 2b trial. Lancet 387, 1178–1186. doi: 10.1016/S0140-6736(16)00082-9
44. Gu, J., Noe, A., Chandra, P., Al-Fayoumi, S., Ligueros-Saylan, M., Sarangapani, R., et al. (2010). Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi). J. Clin. Pharmacol. 50, 401–414. doi: 10.1177/0091270009343932
45. Dubey, A., Yadav, P., Verma, P., & Kumar, R. (2022). Investigation of Proapoptotic Potential of Ipomoea carnea Leaf Extract on Breast Cancer Cell Line. Journal of Drug Delivery and Therapeutics, 12(1), 51-55.
46. Kumar, S., Kumar, A., Kumar, R., Kumar, V., Kumar, N., & Tyagi, A. (2022). Phytochemical, Pharmacognostical and Pharmacological Activities of Carica papaya. International Journal for Research in Applied Sciences and Biotechnology, 9(2), 310-315.
47. Gupta, D. K., Daniels, L. B., Cheng, S., deFilippi, C. R., Criqui, M. H., Maisel, A. S., et al. (2017). Differences in natriuretic peptide levels by race/ethnicity (from the multi-ethnic study of atherosclerosis). Am. J. Cardiol. 120, 1008–1015. doi: 10.1016/j.amjcard.2017.06.030
48. Gupta, D. K., de Lemos, J. A., Ayers, C. R., Berry, J. D., and Wang, T. J. (2015b). Racial differences in natriuretic peptide levels: the dallas heart study. JACC Heart Fail. 3, 513–519. doi: 10.1016/j.jchf.2015.02.008
49. Sahana, S., Kumar, R., Nag, S., Paul, R., Chatterjee, I., & Guha, N. (2020). A REVIEW ON ALZHEIMER DISEASE AND FUTURE PROSPECTS.
50. Nyarko, R. O., Prakash, A., Kumar, N., Saha, P., & Kumar, R. (2021). Tuberculosis a globalized disease. Asian Journal of Pharmaceutical Research and Development, 9(1), 198-201.
51. Hashimoto, Y., Nakao, K., Hama, N., Imura, H., Mori, S., Yamaguchi, M., et al. (1994). Clearance mechanisms of atrial and brain natriuretic peptides in rats. Pharm. Res. 11, 60–64. doi: 10.1023/A:1018941626731
52. Hegde, L. G., Yu, C., Renner, T., Thibodeaux, H., Armstrong, S. R., Park, T., et al. (2011). Concomitant angiotensin AT1 receptor antagonism and neprilysin inhibition produces omapatrilat-like antihypertensive effects without promoting tracheal plasma extravasation in the rat. J. Cardiovasc. Pharmacol. 57, 495–504. doi: 10.1097/FJC.0b013e318210fc7e
53. Bind, A., Das, S., Singh, V. D., Kumar, R., Chourasia, A., & Saha, P. NATURAL BIOACTIVES FOR THE POTENTIAL MANAGEMENT OF GASTRIC ULCERATION. Turkish Journal of Physiotherapy and Rehabilitation, 32, 3.
54. Hodgson-Zingman, D. M., Karst, M. L., Zingman, L. V., Heublein, D. M., Darbar, D., Herron, K. J., et al. (2008). Atrial natriuretic peptide frameshift mutation in familial atrial fibrillation. N. Engl. J. Med. 359, 158–165. doi: 10.1056/NEJMoa0706300

55. Hohl, M., Wagner, M., Reil, J. C., Muller, S. A., Tauchnitz, M., Zimmer, A. M., et al. (2013). HDAC4 controls histone methylation in response to elevated cardiac load. J. Clin. Invest. 123, 1359–1370. doi: 10.1172/JCI61084
56. Holmes, S. J., Espiner, E. A., Richards, A. M., Yandle, T. G., and Frampton, C. (1993). Renal, endocrine, and hemodynamic effects of human brain natriuretic peptide in normal man. J. Clin. Endocrinol. Metab. 76, 91–96. doi: 10.1210/jcem.76.1.8380606
57. Holtwick, R., van Eickels, M., Skryabin, B. V., Baba, H. A., Bubikat, A., Begrow, F., et al. (2003). Pressure-independent cardiac hypertrophy in mice with cardiomyocyte-restricted inactivation of the atrial natriuretic peptide receptor guanylyl cyclase-A. J. Clin. Invest. 111, 1399–1407. doi: 10.1172/JCI17061
58. Hunt, P. J., Espiner, E. A., Nicholls, M. G., Richards, A. M., and Yandle, T. G. (1996). Differing biological effects of equimolar atrial and brain natriuretic peptide infusions in normal man. J. Clin. Endocrinol. Metab. 81, 3871–3876. doi: 10.1210/jcem.81.11.8923831
59. Ibebuogu, U. N. I, Gladysheva, P., Houng, A. K., and Reed, G. L. (2011). Decompensated heart failure is associated with reduced corin levels and decreased cleavage of pro-atrial natriuretic peptide. Circ. Heart Fail. 4, 114–120. doi: 10.1161/CIRCHEARTFAILURE.109.895581
60. Ibrahim, N. E., McCarthy, C. P., Shrestha, S., Gaggin, H. K., Mukai, R., Szymonifka, J., et al. (2019). Effect of neprilysin inhibition on various natriuretic peptide assays. J. Am. Coll. Cardiol. 73, 1273–1284. doi: 10.1016/j.jacc.2018.12.063
61. Iwata, N., Tsubuki, S., Takaki, Y., Watanabe, K., Sekiguchi, M., Hosoki, E., et al. (2000). Identification of the major Abeta1-42-degrading catabolic pathway in brain parenchyma: suppression leads to biochemical and pathological deposition. Nat. Med. 6, 143–150. doi: 10.1038/72237
62. Januzzi, J. L. Jr., Prescott, M. F., Butler, J., Felker, G. M., Maisel, A. S., McCague, K., et al. (2019). Association of change in N-terminal Pro-B-Type natriuretic peptide following initiation of Sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. JAMA 322, 1085–1095. doi: 10.1001/jama.2019.12821
63. Jaski, B. E., Jessup, M. L., Mancini, D. M., Cappola, T. P., Pauly, D. F., Greenberg, B., et al. (2009). Calcium upregulation by percutaneous administration of gene therapy in cardiac disease (CUPID Trial), a first-in-human phase 1/2 clinical trial. J. Card. Fail. 15, 171–181. doi: 10.1016/j.cardfail.2009.01.013
64. Jessup, M., Greenberg, B., Mancini, D., Cappola, T., Pauly, D. F., Jaski, B., et al. (2011). Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID): a phase 2 trial of intracoronary gene therapy of sarcoplasmic reticulum Ca2+-ATPase in patients with advanced heart failure. Circulation 124, 304–313. doi: 10.1161/CIRCULATIONAHA.111.022889
65. Dubey, A., Yadav, P., Verma, P., & Kumar, R. (2022). Investigation of Proapoptotic Potential of Ipomoea carnea Leaf Extract on Breast Cancer Cell Line. Journal of Drug Delivery and Therapeutics, 12(1), 51-55.
66. Saha, P., Kumar, R., Nyarko, R. O., Kahwa, I., & Owusu, P. (2021). HERBAL SECONDARY METABOLITE FOR GASTRO-PROTECTIVE ULCER ACTIVITY WITH API STRUCTURES.
67. Roshan, K. (2020). Priya damwani, Shivam kumar, Adarsh suman, Suthar Usha. An overview on health benefits and risk factor associated with coffee. International Journal Research and Analytical Review, 7(2), 237-249.

68. Sahana, S. (2020). Roshan kumar, Sourav nag, Reshmi paul, Nilayan guha, Indranil Chatterjee. A Review on Alzheimer disease and future prospects. World Journal of Pharmacy and Pharmaceutical science, 9(9), 1276-1285.
69. Kangawa, K., and Matsuo, H. (1984). Purification and complete amino acid sequence of alpha-human atrial natriuretic polypeptide (alpha-hANP). Biochem. Biophys. Res. Commun. 118, 131–139. doi: 10.1016/0006-291X(84)91077-5
70. Kawakami, R., Lee, C. Y. W., Scott, C., Bailey, K. R., Schirger, J. A., Chen, H. H., et al. (2018). A human study to evaluate safety, tolerability, and cyclic GMP activating properties of cenderitide in subjects with stable chronic heart failure. Clin. Pharmacol. Ther. 104, 546–552. doi: 10.1002/cpt.974
71. Kehat, I., Davis, J., Tiburcy, M., Accornero, F., Saba-El-Leil, M. K., Maillet, M., et al. (2011). Extracellular signal-regulated kinases 1 and 2 regulate the balance between eccentric and concentric cardiac growth. Circ. Res. 108, 176–183. doi: 10.1161/CIRCRESAHA.110.231514
72. Kenny, A. J., Bourne, A., and Ingram, J. (1993). Hydrolysis of human and pig brain natriuretic peptides, urodilatin, C-type natriuretic peptide and some C-receptor ligands by endopeptidase-24.11. Biochem. J. 291(Pt 1), 83–88. doi: 10.1042/bj2910083
73. Nyarko, R. O., Kumar, R., Sharma, S., Chourasia, A., Roy, A., & Saha, P. (2022). ANTIBACTERIAL ACTIVITY OF HERBAL PLANT-TINOSPORA CORDIFOLIA AND CATHARNTHUS ROSEUS.
74. Khalil, A. M., Guttman, M., Huarte, M., Garber, M., Raj, A., Rivea Morales, D., et al. (2009). Many human large intergenic noncoding RNAs associate with chromatin-modifying complexes and affect gene expression. Proc. Natl. Acad. Sci. U.S.A. 106, 11667–11672. doi: 10.1073/pnas.0904715106
75. Kishimoto, I., Dubois, S. K., and Garbers, D. L. (1996). The heart communicates with the kidney exclusively through the guanylyl cyclase-A receptor: acute handling of sodium and water in response to volume expansion. Proc. Natl. Acad. Sci. U.S.A. 93, 6215–6219. doi: 10.1073/pnas.93.12.6215
76. Sahana, S. (2020). Purabi saha, Roshan kumar, Pradipta das, Indranil Chatterjee, Prasit Roy, Sk Abdur Rahamat. A Review of the 2019 Corona virus (COVID-19) World Journal of Pharmacy and Pharmaceutical science, 9(9), 2367-2381.
77. Knowles, J. W., Esposito, G., Mao, L., Hagaman, J. R., Fox, J. E., Smithies, O., et al. (2001). Pressure-independent enhancement of cardiac hypertrophy in natriuretic peptide receptor A-deficient mice. J. Clin. Invest. 107, 975–984. doi: 10.1172/JCI11273
78. Knowlton, K. U., Baracchini, E., Ross, R. S., Harris, A. N., Henderson, S. A., Evans, S. M., et al. (1991). Co-regulation of the atrial natriuretic factor and cardiac myosin light chain-2 genes during alpha-adrenergic stimulation of neonatal rat ventricular cells. Identification of cis sequences within an embryonic and a constitutive contractile protein gene which mediate inducible expression. J. Biol. Chem. 266, 7759–7768. doi: 10.1016/S0021-9258(20)89515-5
79. Koepke, J. P., Tyler, L. D., Trapani, A. J., Bovy, P. R., Spear, K. L., Olins, G. M., et al. (1989). Interaction of non-guanylate cyclase-linked atriopeptin receptor ligand and endopeptidase inhibitor in conscious rats. J. Pharmacol. Exp. Ther. 249, 172–176.
80. Koivisto, E., Kaikkonen, L., Tokola, H., Pikkarainen, S., Aro, J., Pennanen, H., et al. (2011). Distinct regulation of B-type natriuretic peptide transcription by p38 MAPK isoforms. Mol. Cell. Endocrinol. 338, 18–27. doi: 10.1016/j.mce.2011.02.015
81. Koller, K. J., and Goeddel, D. V. (1992). Molecular biology of the natriuretic peptides and their receptors. Circulation 86, 1081–1088. doi: 10.1161/01.CIR.86.4.1081

82. Kong, Y., Tannous, P., Lu, G., Berenji, K., Rothermel, B. A., Olson, E. N., et al. (2006). Suppression of class I and II histone deacetylases blunts pressure-overload cardiac hypertrophy. Circulation 113, 2579–2588. doi: 10.1161/CIRCULATIONAHA.106.625467
83. Umama, Y., Venkatajah, G., Shourabh, R., Kumar, R., Verma, A., Kumar, A., & Gayoor, M. K. (2019). Topic-The scenario of pharmaceuticals and development of microwave as; sisted extraction technique. World J Pharm Pharm Sci, 8(7), 1260-1271
84. Singh, M. K., Kumar, A., Kumar, R., Kumar, P. S., Selvakumar, P., & Chourasia, A. (2022). Effects of Repeated Deep Frying on Refractive Index and Peroxide Value of Selected Vegetable Oils. International Journal for Research in Applied Sciences and Biotechnology, 9(3), 28-31.
85. Roshan, K. (2020). Priya damwani, Shivam kumar, Adarsh suman, Suthar Usha. An overview on health benefits and risk factor associated with coffee. International Journal Research and Analytical Review, 7(2), 237-249
86. Sahana, S. (2020). Roshan kumar, Sourav nag, Reshmi paul, Nilayan guha, Indranil Chatterjee. A Review on Alzheimer disease and future prospects. World Journal of Pharmacy and Pharmaceutical science, 9(9), 1276-1285.
87. Nyarko, R. O., Kumar, R., Sharma, S., Chourasia, A., Roy, A., & Saha, P. (2022). ANTIBACTERIAL ACTIVITY OF HERBAL PLANT-TINOSPORA CORDIFOLIA AND CATHARNTHUS ROSEUS.
88. Kumar, R., Saha, P., Lokare, P., Datta, K., Selvakumar, P., & Chourasia, A. (2022). A Systemic Review of Ocimum sanctum (Tulsi): Morphological Characteristics, Phytoconstituents and Therapeutic Applications. International Journal for Research in Applied Sciences and Biotechnology, 9(2), 221-226.
89. Kurtz, A., Della Bruna, R., Pfeilschifter, J., Taugner, R., and Bauer, C. (1986). Atrial natriuretic peptide inhibits renin release from juxtaglomerular cells by a cGMP-mediated process. Proc. Natl. Acad. Sci. U.S.A. 83, 4769–4773. doi: 10.1073/pnas.83.13.4769
90. Kuwahara, K., Kinoshita, H., Kuwabara, Y., Nakagawa, Y., Usami, S., Minami, T., et al. (2010). Myocardin-related transcription factor A is a common mediator of mechanical stress- and neurohumoral stimulation-induced cardiac hypertrophic signaling leading to activation of brain natriuretic peptide gene expression. Mol. Cell. Biol. 30, 4134–4148. doi: 10.1128/MCB.00154-10
91. Lako-Futo, Z., Szokodi, I., Sarman, B., Foldes, G., Tokola, H., Ilves, M., et al. (2003). Evidence for a functional role of angiotensin II type 2 receptor in the cardiac hypertrophic process in vivo in the rat heart. Circulation 108, 2414–2422. doi: 10.1161/01.CIR.0000093193.63314.D9
92. Nyarko, R. O., Kumar, R., Sharma, S., Chourasia, A., Roy, A., & Saha, P. (2022). ANTIBACTERIAL ACTIVITY OF HERBAL PLANT-TINOSPORA CORDIFOLIA AND CATHARNTHUS ROSEUS
93. Kumar, R., Saha, P., Lokare, P., Datta, K., Selvakumar, P., & Chourasia, A. (2022). A Systemic Review of Ocimum sanctum (Tulsi): Morphological Characteristics, Phytoconstituents and Therapeutic Applications. International Journal for Research in Applied Sciences and Biotechnology, 9(2), 221-226.
94. Bind, A., Das, S., Singh, V. D., Kumar, R., Chourasia, A., & Saha, P. NATURAL BIOACTIVES FOR THE POTENTIAL MANAGEMENT OF GASTRIC ULCERATION. Turkish Journal of Physiotherapy and Rehabilitation, 32, 3.

95. Singh, M. K., Kumar, A., Kumar, R., Kumar, P. S., Selvakumar, P., & Chourasia, A. (2022). Effects of Repeated Deep Frying on Refractive Index and Peroxide Value of Selected Vegetable Oils. International Journal for Research in Applied Sciences and Biotechnology, 9(3), 28-31.