NATURALISTA CAMPANO
ISSN: 1827-7160
Volume 28 Issue 1, 2024

Investigation of Anti-Hyperlipidemic and Anti-diabetic Activity of Nimbin in Wistar Rat

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Abstract: Finding out whether Nimbin anti-hyperlipidemic and Anti-diabetic Activity effects are at work when administered orally in doses of 2 or 4 mg was the driving force for this study. Hyperlipidemia is becoming more common at a frightening pace. Hyperlipidemia is a medical condition that is rapidly becoming more common. At the present rate of rise, one-third of the population will have diabetes by 2050, and hyperlipidemia will impact almost 30 million Americans by the same year. We tested the anti-hyperlipidemic activity using the Dexamethasone and Triton induced hyperlipidemia paradigm. Oral dosage of 4 mg/kg is more efficacious than oral administration of 2 mg/kg in cases of hyperlipidemia. Nimbin shows promising anti-hyperlipidemic benefits when given intramuscularly at doses of 2 or 4 mg/kg, as shown in the trials.

Keywords- Hyperlipidemia, Triton, Dexamethasone, Diabetes, Nimbin.

1. Background

Hyperlipidemia is a condition that affects lipid metabolism, and the present global trend indicates that the incidence of hyperlipidemia is on the rise more frequently. An extensive number of studies [1, 2] have demonstrated that hyperlipidemia and cardiovascular diseases (CVD) are significantly linked to one another. High levels of the lipoprotein LDL-cholesterol, also known as LDL-c, have been linked to an increased likelihood of developing coronary heart disease (CHD) and atherosclerosis (AS) [3, 4]. Both of these disorders can be identified by the presence of elevated levels of triglycerides (TG) and free fatty acids (FFA) in the blood [5, 6]. These elevated levels are extremely important to both of these cases. It is therefore believed that the most successful approaches for treating and preventing cardiovascular disease are those that include lowering elevated blood levels of total cholesterol, total fat, and LDL-c, as well as managing dysregulation of lipid metabolism. It is [7] that is the correct answer.
Peroxisome proliferator-activated receptor alpha (PPARα) has been shown to have a significant role in the regulation of lipid metabolism, as indicated by a multitude of research [8, 9, 10]. The expression of genes involved in the transport and oxidation of fatty acids, such as acyl-CoA oxidase (ACO) [11], [12], carnitine palmitoyl transferase 1 (CPT1) [13], [14], [15], fatty acid transport protein (FATP) [16], [17], hormone-sensitive lipase (HSL) [18], [19], and lipoprotein lipase (LPL) [20], [21], is enhanced when ligands activate

PPARε. The activation of PPARα results in a modification of gene transcription, which in turn leads to enhancements in the breakdown of triglycerides and fatty acids, enhancements in the cellular absorption of fatty acids, and a reduction in the synthesis of triglycerides and fatty acids. The PPAR-regulated gene LPL is responsible for limiting the pace at which the TG cores of circulating TG-rich lipoproteins, such as chylomicrons and very low-density lipoproteins (VLDL), are hydrolyzed [22], [23]. This gene is responsible for encoding the hydrolysis of the TG core, which is the phase in the TG metabolism process that is the rate-limiting step. LPL not only lowers levels of VLDL by eliminating TG, but it also increases the amount of LDL that is taken up by the body by establishing links between the cell surface and lipoproteins. As a result of this, LPL contributes to the elimination of VLDL and LDL from the bloodstream according to [24]. There have been multiple studies that have demonstrated that fenofibrate, which is classified as a PPARα agonist, has the ability to increase the hypotriglyceridemic effects of its class by promoting the production and activity of lipoprotein lipase (LPL) [25], [26]. AMP-activated protein kinase (AMPK) is an additional critical regulator of lipid metabolism [27, [28], [29]. This is due to the fact that it exerts a significant influence on the oxidation, synthesis, and storage of lipids. Through the activation of a pathway that generates ATP, such as lipid oxidation, the activation of AMPK inhibits processes that require a significant amount of energy, such as glucose production and protein synthesis, respectively. It is possible to determine whether or not AMPK is active by observing the phosphorylation of the alpha-subunit at threonine (Thr-172). According to the information that was presented in [30], this phosphorylation results in the inhibition of acetyl-CoA carboxylase (ACC), which is an enzyme that plays a significant role in regulating the generation and oxidation of fatty acids. In recent years, there has been a growing interest in the AMPK pathway as a potential therapy target for obesity and metabolic illnesses associated with it, such as hyperlipidemia [27]. The blood contains high levels of total cholesterol (TC), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL), in addition to low levels of high-density lipoprotein (HDL). Hyperlipidemia is characterised by the presence of these three types of lipoproteins. Based on the definition provided by the American Heart Association, hyperlipidemia is a clinical condition that occurs when the levels of triglycerides and cholesterol in the blood are unusually high. These lipids are constructed from triglycerides and cholesterol, which are the fundamental components underlying their formation. When there is a high concentration of lipids and fatty molecules in the blood, the risk of developing atherosclerosis and cardiovascular disease is increased. In regard to both the first and the second If you are experiencing any of the following symptoms, you should get medical attention as soon as possible: high blood pressure, pancreatitis, xanthomas, gallstones, coronary artery disease (CAD), or gallstones. It is important to note that hyperlipidemia, which is one of the most significant alternative illnesses, is developing along with these challenges.[30] Coronary artery disease is expected to surpass all other causes of death by the year 2020, particularly in India. This prediction applies to the entire world.[35][36] Circulatory artery disease (CAD) is associated with a number of adverse effects, and hyperlipidemia is one of those results. This condition manifests itself when the arterial wall reacts excessively to a number of potentially damaging stimuli. The section three and section four It is our belief that the Azadirachta indica plant originated in either Central America, Africa, or India at some point in its lengthy history. The lightning-fast growth rate of this annual plant is one of its defining characteristics. [37]"Neem tree for resolving global concerns" was the title of a publication that was released in 1992 by the United States Scientific Community and addressed issues related to the environment. [38,39] It became clear that the Neem tree is of critical significance throughout the course of our inquiry. According to reports, a comprehensive analysis of the current state of research on neem has been published in other publications. [40-42] It has been demonstrated that neem has a number of diverse naturally occurring combinations that, when generated on purpose, have a significant lot of favourable benefits on therapeutic applications.[43] According to the findings of German experts, the ability of neem to prevent cavities and periodontal disease is responsible for a healthy smile to be achieved. The effectiveness of the antibacterial capabilities of neem leaf extract against a wide range of pathogens, such as Candida albicans and Enterococcus faecalis, has been proven via numerous studies [44-45]

2. Material & Methods

Experimental Rodents

Male and female Wistar rats ranging in weight from 150 to 200 grammes were utilized in the study. They were obtained in accordance with the regulations set forth by the IAEC. Each pen contained three animals housed in polypropylene, and a temperature of 28 ± 50 degrees Celsius was maintained. Additionally, the animals were subjected to a twelve-hour light-dark cycle. Instead of water, the animal was given food pellets created by Hindustan Lever so it could get the proper treatment. The animals were fasted for a long period before the evaluation, and the study was approved for animal concerns by the IAEC (1122/PO/Re/S/20/CPCSEA). The investigation's use of all structures was covered by this approval. [8]

Chemicals and Drugs
Nimbin and Triton were supplied by Sigma-Aldrich, and Dexamethasone Phosphate Injection (Neon Laboratories Limited, Andheri East Mumbai, Batch No. SLDS-318) and Gemfibrozil (Batch No. - 7456280072) were provided by Pfizer Pharmaceutical.

3. Study Design
Induction of diabetes
The administration of a single intraperitoneal (i.p.) injection of freshly produced streptozotocin 60 mg/kg body weight in 0.1 M citrate buffer (pH 4.5) in a volume of 0.5 ml/kg body weight was necessary in order to induce diabetes in rats that had been fasted for the previous 24 hours. On the fifth day after STZ treatment, the level of glucose in the blood was measured while the patient was fasting. This proved that diabetes had been induced. Rats that had a fasting blood glucose level that was more than 200 mg/dl were regarded to be diabetes and were used in the experiment [9,17,28]

Hyperlipidemia that triggered in rats by 1- dexamethasone
An increase in hyperlipidemia will occur as a consequence of the use of dexamethasone, which is a glucocorticoid that is known to cause this rise in plasma lipid levels. In order to have an effect on hyperlipidemia, dexamethasone was administered intracutaneously to Wistar rats at a dose of 10 milligram's per kilograms on a daily basis for a period of eight days. A total of six (n=6) wistar rodents were included in each of the five groups of species that were encountered. These groupings were formed out of the creatures who were divided. [29][30]

Group 1 (the normal control) received a normal saline solution.
Group 2 (the hyperlipidemic control) received a normal saline solution.
Group 3 (the standard group) received gemfibrozil 10 milligrams per kilogram per day suspended in gum acacia in water.
Group 4 (the test group-I) received Nimbin 2 milligrams per kilogram orally.
Group 5 (the test group-II) received Nimbin 4 milligrams per kilogram orally.

The administration of a series of subcutaneous injections of dexamethasone at a dose of ten milligram's per kilograms per day was carried out for a period of eight days in order to induce hyperlipidemia in each of the four groups of rats. Normal saline was administered to the animals that were a part of the control group for normal hyperlipidemia throughout the course of the experiment that lasted for a total of eight straight days. Gemfibrozil was given to the individuals in Group III at a dosage of 10 mg/kg/day, and it was injected intraperitoneally in a suspension of gum acacia water. The individuals in Groups IV and V were given nimbin through oral administration at doses of 2 mg/kg/day and 4 mg/kg/day, respectively. This was done in order to measure the effects of the drug.
The experimental mice that had been permitted to go without food for a whole night were sacrificed by being beheaded while under the effect of light ether anesthesia. This was done in order to ensure that the outcome of the experiment was accurate. Following completion of the experiment, blood was taken from the participants. The extraction of serum made it feasible to conduct an examination of lipid profiles, which are a variety of different sorts of biochemical features [32] [33].

Triton induced hyperlipidemia
On a daily basis, a single dose of either the standard drug or the test drug was administered to each of the rats, who were then separated into five groups, each of which contained six rats.

Group- I is the normal control.
Group- II Hyperlipidemic control is the focus of Triton (100 mg / kg)] i.p.
Group- III received a standard dose of gemfibrozil (10 mg/kg) orally.
Group- IV Nimbin, two milligrams per kilogram, orally administered to the group.
Group-V Nimbin, four milligrams per kilogram, orally, was administered
In order to generate hyperlipidemia, a single intraperitoneal injection of a newly manufactured solution of Triton X-100 (100 mg/ kg) in physiological solution was given to the patient after they had fasted for 18 hours while fasting overnight. This was done in order to induce hyperlipidemia. This study was carried out over the length of seven days, and the protocol for this study was also carried out over the duration of seven days from start to finish. A retro orbital sinus puncture was performed on the patient while they were under a general anesthesia of moderate ether. This was done after the eighth day of treatment, which was also the day after an

injection of triton X-100 that had been administered for 18 hours. In order to get serum, blood samples were immediately centrifuged in an ultra-cool centrifuge at a speed of 3000 revolutions per minute for fifteen minutes at room temperature. This was done in order to obtain serum. Measurements of plasma were taken with the assistance of an enzymatic sample kit. [8] [35] [36]

Biochemical Estimation of Blood Serum

The levels of plasma lipids, which include total cholesterol, total fat, high-density lipoprotein (HDL), very low density lipoprotein (VLDL), and low-density lipoprotein (LDL), were evaluated by utilizing serum samples and diagnostic commercial kits from Qualigens diagnostic Mumbai, India. These kits were purchased from the company. When doing the examination on the samples, a semiautomatic analyzer was utilized as the instrument of choice. [37][38]

Glycosylated hemoglobin, liver glycogen and histopathological analysis

For the purpose of determining the amount of glycosylated hemoglobin present, blood was also collected in EDTA tubes from the retro-orbital sinus while the patient was under ether anesthesia at the conclusion of the treatment period. Immediately following the collection of blood, the animals were slaughtered by dislocating their cervical vertebrae while under the influence of ether. The liver and pancreas were then separated and subjected to histological examination. The glycogen content of a portion of the liver tissue that had been extracted was determined using the procedure that was described before.

Statistical Analysis

In order to carry out the statistical analysis, the software known as Graph pad 5.0 was utilized. S.E.M., which stands for standard error of the mean, was used to conduct the statistical study. Through the utilization of Dunnett's test and frequency analysis (ANOVA), we were able to investigate the statistical significance of differences between the groups. Comparisons with a significance level of $P \leq 0.05$ were deemed to be statistically significant.

4. Results & Discussion

Total cholesterol and Total triglycerides in patients with hyperlipidemia caused by dexamethasone

The group that was induced with hyperlipidemia has had a considerable increase in the total cholesterol levels when compared to the rates that were observed in the normal rats. When compared to Group I, which is the normal rodent group, the results were determined to be within the range of 65.43± 0.933 mg/dl. However, when compared to the values, the levels had increased to 118.71 ± 1.329 miligrams per deciliter. Consequently, hypercholesterolemia is a condition that exists. The values of the treatment group that was administered with Nimbin (2mg/kg) or Nimbin (4mg/kg) were lowered to 85.23 ± 1.046 ($P< 0.001$) and 83.35 ± 0.885mg/dl ($P< 0.0001$), respectively, in a systematic manner. This reduction was observed in both the treatment group and the control group. Those patients who underwent the nimbin treatment experienced a considerable decrease in their overall cholesterol levels during the course of the study. Nevertheless, it is important to mention that Gemfibrozil has also shown a noteworthy decrease in blood total cholesterol levels, with the levels reaching 74.70 ± 0.794 mg/dl ($P< 0.001$). [The first table]. The group that was induced by dexamethasone has reported that the levels of triglycerides (TG) have increased to a level of 150.71 milligrammes per deciliter, with a standard deviation of 0.518 milligrammes. Taking into consideration the normal rats, the readings are 63.75 ± 0.507 mg/dl. This is a comparison to the normal rats. Triglycerideemia can be inferred from this evidence. The readings were dramatically reduced to 79.50 ± 0.526 milligrammes per kilogramme ($P<0.001$) and 75.25 ± 0.641 milligrammes per deciliter ($P<0.0001$), respectively, in the group that was given Nimbin at a dosage of 2 milligrammes per kilogramme or 4 milligrammes per kilogramme. This was a statistically significant decrease. The readings were found to fall to 68.33 ± 0.572 mg/dl ($P<0.001$) within the group that was treated with Gemfibrozil, which is referred to as the Standard Group. [table 1].

Results with high-density lipoprotein cholesterol brought forth by the administration of dexamethasone

The high density that contains cholesterol, which is a lipid protein, has been greatly reduced in a group that was induced with dexamethasone in contrast to the normal rats group. This was observed in the rats. The readings have decreased to 25.75 ± 0.410 miligrams per kilogramme, which is a significant decrease when compared to the normal rat group, which had a standard deviation of 41.68 ± 0.795 mg/dl. Nimbin was administered to some members of the group at a dosage of either 2 mg/kg or 4 mg/kg in order to safeguard them. According to the findings, the levels were found to be 65.79 ± 0.602 ($P<0.001$) and 29.40 ± 0.517 mg/dl ($P<0.0001$),

respectively. Based on the data presented in Table-1, the results obtained in the group that was administered Gemfibrozil (Std.Group) were 35.50 ± 0.665 mg/dl (P<0.001).

LDL-cholesterol and VLDL-cholesterol levels were caused by the administration of dexamethasone
In the group that was provoked with dexamethasone, the amount of LDL cholesterol increased to 57.32 ± 0.811 mg/dl. This was in contrast to the normal rat group, which had a level of 15.59 ± 0.495 mg/dl throughout the study. In some of the individuals, the administration of Nimbin at doses of 2 mg/kg and 4 mg/kg was sufficient to protect them.Upon examination, it was observed that the levels of 34.67 ± 0.609 (P<0.001) and 25.73 ± 0.551 mg/dl (P<0.0001) exhibited a decrease. It was discovered that the group that was given nimbin therapy had much lower levels of LDL cholesterol than the other group. Based on the data presented in Table-1, it is evident that gemfibrozil has significantly reduced levels of LDL cholesterol to 24.35 ± 0.563 mg/dl (P<0.001).When compared to the normal rat group, which had a VLDL-cholesterol level of 14.42 ± 0.455 mg/dl, the dexamethasone-induced group had a VLDL-cholesterol level of 39.42 ± 0.650 mg/dl, which is a significant increase. In some of the individuals, the administration of Nimbin at doses of 2 mg/kg and 4 mg/kg was sufficient to protect them. Following the measurements, it was shown that there was a decrease of 31.60 ± 0.441 (P<0.001) and 24.80 ± 0.505 mg/dl (P<0.0001), accordingly. A substantial decrease in nimbin levels was seen in the group that was the recipient of therapy. As can be seen in Table-1, the administration of gemfibrozil has resulted in a significant reduction in the concentration of VLDL-cholesterol, which has reached 18.75 ± 0.527 mg/dl (P<0.001).

Dexamethasone induced results of atherogenic index

$$\text{Atherogenic index} = \frac{\text{Total serum cholesterol}}{\text{Total serum High density containing lipid protein-cholesterol}}$$

The atherogenic index of the dexamethasone-induced group hyperlipidemia control group is 5.89, which is significantly higher than the atherogenic index of the normal rat group, which is 1.589. This indicates that the atherogenic index has significantly increased. When Nimbin was administered at a dosage of either 2 mg/kg or 4 mg/kg, the values were dramatically lowered to 2.26 and 1.89, respectively, in the group that was prevented from experiencing the condition. A considerable decrease in the values of 3.13 has occurred as a consequence of the administration of gemfibrozil [Table1].

Table 1 Effect of Nimbinin Dexamethasone injection induced Hyperlipidemia Wistar Rat

Group	**Treatment /dose**	**Total cholesterol (milligra m/deciliter)**	**Total TG (milligra m/deciliter)**	**High density containing lipid protein (milligram/ deciliter)**	**Low density containing lipid protein (milligram/ deciliter)**	**Very low density containing lipid protein(milligram /deciliter)**	**Ather ogenic index**
I	Normal-group	65.43±0.933	64.75 ±0.711	41.68 ±0.795	15.59±0.495	14.42 ±0.455	1.59
II	Normal-control group	118.71±1.329	151.71±0.518	25.75±0.410	57.32±0.811	39.42±0.650	5.89
III	Standard group Gemfibroz il (10mg/kg)	74.70±794**	69.33±0.572**	35.50±0.665**	24.35 ±.563**	18.75 ±0.527**	3.13
IV	Test group-I Nimbin (2mg/kg) –I	85.23±.046**	79.50±0.526**	26.79±0.602**	34.67±0.609**	31.60 ±0.441**	2.26

V	Test group-II Nimbin(50mg/kg)	83.35±0.885***	76.25± 0.641***	29.40 ± 0.517***	25.73 ± 0.55***	24.80±0.505***	1.89

There is a correlation between increases in the levels of the hormone glucocorticoid and the concentration of lipids in plasma; however, the nature of this correlation varies from species to species. Glucocorticoids, when injected into mice, induce the creation of a small quantity of triglycerides in the liver. This takes place when the glucocorticoids are administered. This, in turn, might effectively lead to the buildup of fatty liver tissue inside the liver. An increase in the secretion of very low density lipoprotein (VLDL) could be the outcome of the stimulation of the formation of good cholesterol (TG). There is a chance that the amount of very low density lipoprotein (VLDL) produced by rodents might grow if they were administered dexamethasone for a period of many days. The condition known as hyperlipidemia is brought on by an imbalance in the metabolism of lipids, which is brought on by an increase in those levels of total cholesterol.

Total cholesterol and overall triglycerides were measured as a result of triton-induced hyperlipidemia.
The group that was induced with hyperlipidemia has had a considerable increase in the total cholesterol levels when compared to the rates that were observed in the normal rats. After comparing the values to those of Group I (the normal rodent group), which were determined to be within the range of 65.44± 0.933 mg/dl, the levels had increased to 118.82 ± 1.329 miligrams per kilogramme, which is a substantial rise. Consequently, hypercholesterolemia is a condition that exists. Within the treatment group, Nimbin was given at a dosage of either 2 mg/kg or 4 mg/kg. Both of these numbers were delivered. By employing a systematic approach, the outcomes are lowered to 83.20± 1.046 (P< 0.001) and 82.36± 0.845mg/dl (P< 0.0001), respectively. Those patients who underwent the nimbin treatment experienced a considerable decrease in their overall cholesterol levels during the course of the study. Furthermore, it is important to mention that Gemfibrozil has also been shown to exhibit a noteworthy reduction in the levels of total cholesterol in the blood, with the levels reaching 72.81 ± 0.794 mg/dl (P< 0.001). The second table. When compared to the values in the normal rats, which are 62.66 ± 0.507 mg/dl, the levels of triglycerides (TG) in the group that was triggered by dexamethasone have grown to 151.72 ± 0.528 miligrams per kilogramme. This is a substantial increase. This provides evidence that a diagnosis of triglycerideemia was provided. In the group that was given Nimbin at a dosage of 2mg/kg or 4mg/kg, the values underwent a noteworthy decrease, reaching 78.10 ± 0.521mg/dl (P<0.001) and 75.24 ± 0.631 miligram/deciliter (P<0.0001), respectively. This reduction was statistically significant. The group that was treated with Gemfibrozil, which is referred to as the Standard Group, experienced a decrease in the results, which were found to be 69.30 ± 0.572 mg/dl (P<0.001).

Triton responsible for the high-density lipoprotein cholesterol that was produced.
When compared to the group of rats that the researchers judged to be normal, the levels of HDL cholesterol in the group of rats that were stimulated with dexamethasone were significantly lower than those in the group of rats that were under the control of the researchers. As compared to the normal rat group, which had levels of 41.68 ± 0.784 mg/dl, the readings have now fallen to an average of 23.55 ± 0.410 mg/dl. This represents a considerable decrease in comparison to the earlier readings. In order to ensure the safety of some individuals within the group, Nimbin was given to them at a dosage of either 2 mg/kg or 4 mg/kg. It was established that the results were 24.29 ± 0.603 mg/dl (P<0.001) and 28.40 ± 0.527 mg/dl (P<0.0001) respectively, based on the findings that were obtained. As shown in Table-2, the values obtained from the group that was treated with Gemfibrozil (Std.Group) were 35.50 ± 0.675 mg/dl (P<0.001). These data were obtained from the study conducted by the researchers.

Triton induced results of LDL-cholesterol and VLDL- cholesterol
When compared to the normal rat group, which had a level of 14.58 ± 0.56 mg/dl, the LDL-cholesterol level in a group that was induced with dexamethasone has dramatically increased to 55.20 ± 0.831 mg/dl. This is a considerable increase. Nimbin was administered to some members of the group at a dosage of either 2 mg/kg or 4 mg/kg in order to safeguard them. In terms of the measurements, there was a drop in the values of 31.76 ± 0.609 (P<0.001) and 26.80 ± 0.551 mg/dl (P<0.0001), respectively. There is a discernible decrease in the levels of LDL cholesterol that were assessed in the group that was administered nimbin treatment. The level of LDL cholesterol has been dramatically lowered to 23.34 ± 0.573 mg/dl (P<0.001), as shown in Table 2. It is important to note that gemfibrozil has been responsible for this reduction.In contrast to the normal rat group, which had a VLDL-cholesterol level of 12.91 ± 0.615 mg/dl, the dexamethasone-induced group has had a

substantial increase in their VLDL-cholesterol level, which has reached 39.40 ± 0.650 mg/dl due to the administration of dexamethasone. Nimbin was administered to some members of the group at a dosage of either 2 mg/kg or 4 mg/kg in order to safeguard them.In terms of the findings, it was seen that there was a reduction of 31.20 ± 0.431 (P<0.001) and 25.80 ± 0.525 mg/dl (P<0.0001), respectively. There was a discernible decrease in the levels of nimbin that were seen in the therapy group. As shown in Table-2, it is important to take note that gemfibrozil has resulted in a noteworthy decrease in the level of very low density lipoprotein cholesterol (VLDL-cholesterolto19.64±0.527mg/dl(P<0.001).

Results of the atherogenic index that were caused by triton.

$$\text{Atherogenic index} = \frac{\text{Total serum cholesterol}}{\text{Total serum High density containing lipid protein}}$$

When compared to the normal rat group, which had an atherogenic index of 1.48, the atherogenic index experienced by the dexamethasone-induced group hyperlipidemia control group was increased to 3.78. The values are significantly reduced to 3.04 and 2.88, respectively, in the group that was prevented with Nimbin at a dosage of either 2 mg/kg or 4 mg/kg. A significant reduction in the values of 2.22 has been observed with the use of gemfibrozil [Table2].

Table 2- Effect of Nimbinon Triton induced Hyperlipidemia in Wistar Rat

Group	Treatment/ dose	Total cholesterol (milli gram/ deciliter)	TotalTG (milligram/deciliter)	HDL-Cholesterol (milligram/deciliter)	LDL-Cholesterol (milligram/deciliter)	VLD L-Cholesterol (milligram/deciliter)	Atherogenic index
I	Normal-group	65.44±0.943	62.66±0.621	41.69± 0.784	14.58±0.565	12.91 ±	1.48
II	Normal-control group	118.82± 1.329	151.72±0.528	23.6 ±0.410	55.20±0. 831	39.40±0.640	3.78
III	Standard group Gemfibrozil (10mg/kg)	72.81± 0.794**	69.30±0.582**	35.50±0.675**	23.34±0.573**	19.64 ±0.527**	2.22
IV	Test group -I nimbin (2mg/kg) –I	83.20± 1.046**	78.10±0.521**	24.28±0.603**	31.76±0. 608**	31.20±0.431**	3.04
V	Test group -II nimbin (4mg/ kg)	82.36 ± 0.845 ***	75.24± 0.631***	28.40± 0.527***	26.72 ± 0.405***	25.80± 0.525***	2.88

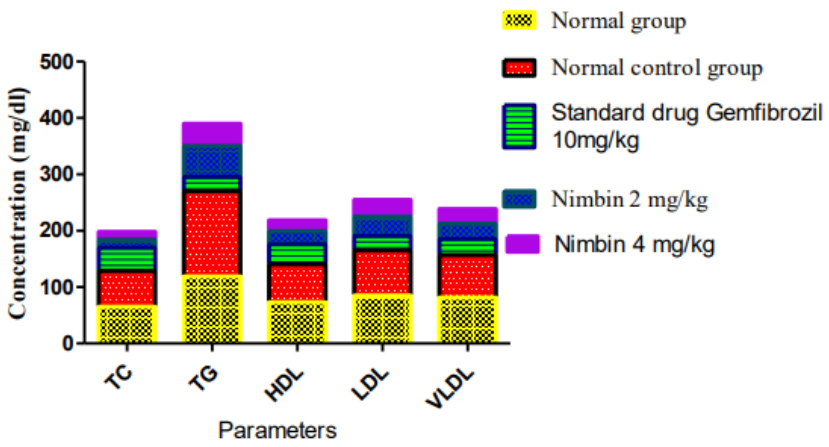

Fig: 1 The effects of 2 mg/kg and 4 mg/kg on dexamethasone-induced hyperlipidemia are depicted in the column graph.

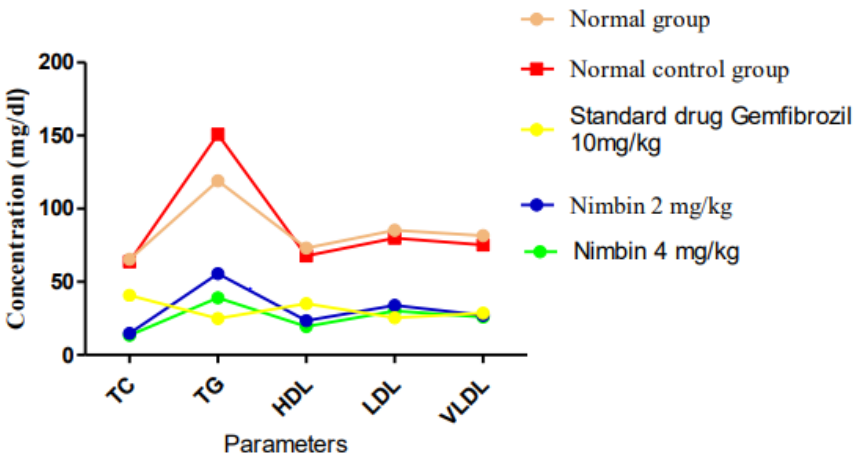

Fig: 2 A Line Graph Displaying the Effect of 2mg/kg & 4mg/kg on Hyperlipidemia Caused by Triton Induction

Patients who suffer from metabolic syndrome, which is a mix of hyperlipidemia, hypertension, and diabetes mellitus, have a higher risk of cardiovascular mortality and morbidity. This is because metabolic syndrome is a combination of these three conditions. Individuals who suffer from all three of these illnesses at the same time are referred to be syndrome-x patients. Chronic coronary heart disease, which is brought on by the advancement of atherosclerosis, is the leading cause of morbidity and mortality across the entire world. This condition has a considerable influence on the levels of total low-density lipoprotein (LDL) and high-density lipoprotein (HDL) in the body. In addition, the aetiology of this disorder is affected by a variety of other factors, including diabetes, hypertension, smoking, glucocorticoids, dietary agents, and psychological issues. These are only some of the elements that can play a role.

Effect of nimbin on histology of Pancreatic

The histological characteristics of the endocrine and exocrine components of the pancreas were found to be intact in the pancreatic sections of normal control rats (Fig. 3). According to figure 3, the injection of streptozotocin led to the production of diabetes, which resulted in moderate histological abnormalities. These changes included necrotic and degenerative changes in the islets of Langerhans, as well as a decrease in the number of β-cells. Based on the comparison between the diabetic control rats and the normal control rats, the damage index (Nos.) of pancreatic tissue increased from 0.00 to 3.62 ± 0.18. This was the outcome of the aforementioned circumstance. As a result of the treatment with OJ, Metformin, and OJ-Metformin, these histological abnormalities were averted (figure 3), which led to a considerable reduction in the damage index of pancreatic tissue (figure 4).

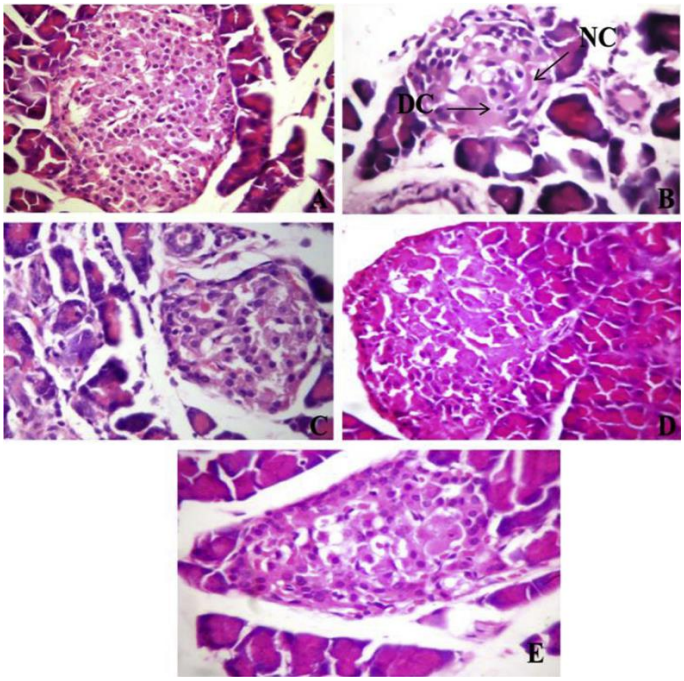

Fig: 3 There are three microscopic images of pancreatic slices that were collected from various groups of animals, and they are displayed in Figure 3. There are regions of abundant β-cells seen in the photos belonging to group A. In group B, the mice who have diabetes have moderate histological abnormalities, which include necrotic and degenerative changes in the islets, as well as the loss of β-cells. Within group C, the diabetic rats that were administered Metformin at a dose of 100 mg/kg exhibited alterations that were either modest or mild. The diabetic rats who were assigned to group D and given nimbin at a dose of 0.28 millilitres per kilogramme twice daily also exhibited alterations that were low to mild. In conclusion, the diabetic rats who were treated simultaneously with nimbin and metformin at a dose of 100 mg/kg had only slight alterations in group E.

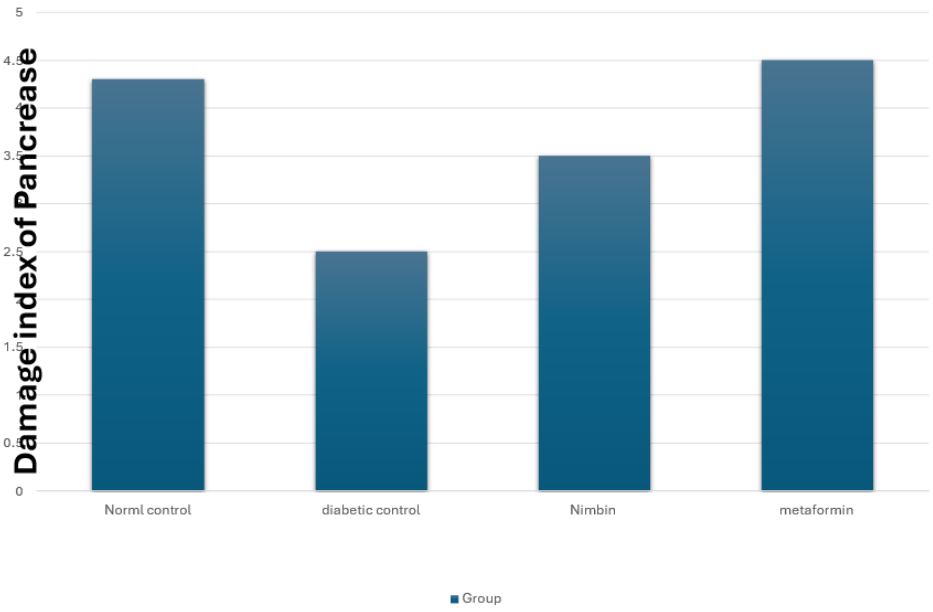

Fig. 4 shows the damage index in the pancreatic segment of both the control group and the treatment class. The p-value is less than 0.001 when compared to the normal control, and it is less than 0.001 when compared to the diabetes control. We compared the values of the diabetes control group with those of the normal control group as well as the values of the drug-treated groups with the diabetic control group.

Effect of nimbin on liver tissue

The liver tissue of normal control rats was examined under a microscope, and the results showed that the histological characteristics were normal (figure 5). Significant pathological alterations were brought about in the liver parenchyma as a result of the induction of diabetes. These changes included cellular edoema with degenerative changes, vacuolar abnormalities, and concentrated areas of bleeding. Based on the comparison between the diabetic control rats and the normal control rats, the damage index (Nos.) of liver tissue increased from 0.00 to 3.75 ± 0.20. This was the result of the aforementioned circumstance. In order to prevent these histological changes (figure 5), treatment with OJ, Metformin, and OJ-Metformin was administered. As a result, the damage index of liver tissue was significantly reduced (figure 6).

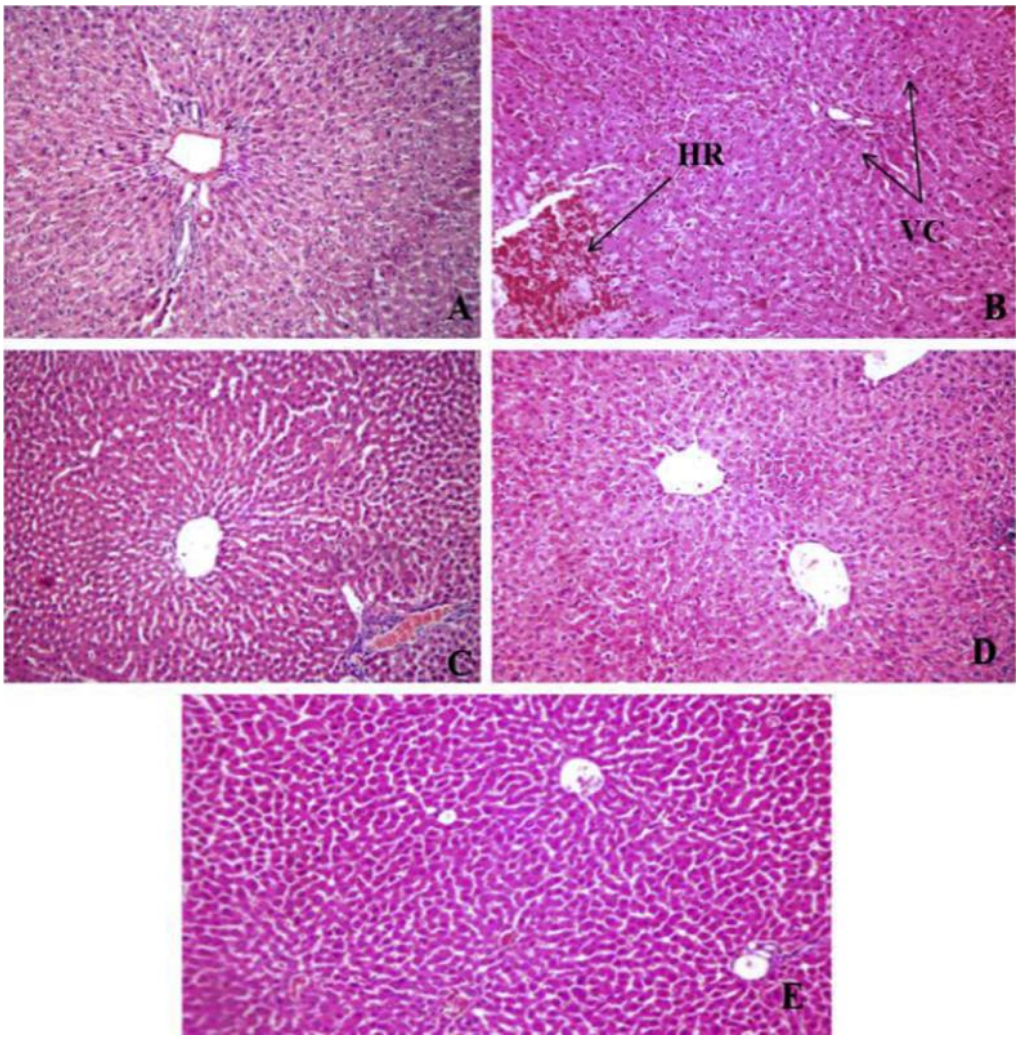

Fig: 5 The following are examples of microscopic images of liver sections taken from different groups of animals: (A) normal control animals, (B) diabetic control animals with moderate pathological changes like haemorrhage and vascular changes of hepatocytes, (C) diabetic animals treated with Metformin at a dose of 100 mg/kg, which showed mild changes, (D) diabetic animals treated with Ojamin at a dose of 0.28 ml/kg, twice daily, which showed minimal to mild changes, and (E) diabetic animals treated simultaneously with both Ojamin and Metformin at a dose of 100 mg/kg, which showed mild to minimal changes (H and E ×100).

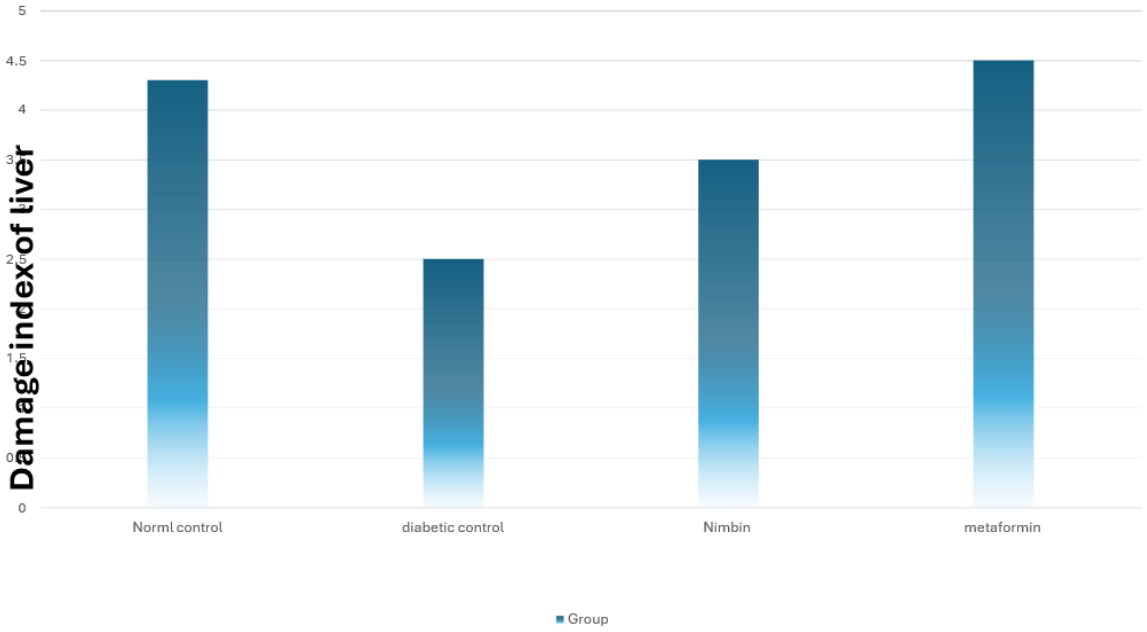

Figure 6 shows the damage index in the liver part of both the control group and the treatment group. The p-value is less than 0.001 when compared to the normal control, and it is less than 0.001 when compared to the diabetes control. We compared the values of the diabetes control group with those of the normal control group as well as the values of the drug-treated groups with the diabetic control group.

5. Conclusion

As a consequence of the widespread application of Triton WR-1339, which is designed to prevent the loss of phospholipids that are rich in triglycerides, a number of different species have experienced transitory hypertriglyceridemia. Following the administration of Triton intravenously, the researchers at Schurr et al. discovered that adult rats developed hyperlipidemia.Taking triton results in a significant increase in the amounts of triglycerides and total cholesterol that are seen in the plasma of the blood. The reason for this is that the liver produces more very low density containing lipid protein, despite the fact that low density containing lipid protein and very low density containing lipid protein are less catabolic. The process by which tissues in the periphery absorb lipoproteins from the bloodstream is facilitated by detergent triton, which prevents phospholipids from interfering with the process altogether. As a consequence of this, the levels of lipids in the body increase. In spite of the fact that the rodent Triton model of hyperlipidemia has a wide range of applications, one of the most prevalent applications for rat analysis is the screening of hypolipidemic medications, which can be either naturally occurring or synthesized. According to the findings, the most effective treatment for hyperlipidemia was administered at a dose of four milligram's per kilograms, which was the higher of the two dose levels that were evaluated. OJ was found to have a substantial impact in lowering blood sugar and cholesterol levels in rats that had diabetes brought on by streptozotocin, as demonstrated by the findings. This is the reason why OJ has the potential to be used as a medicinal agent in the treatment of diabetes. It would appear that the state of diabetes is controlled less efficiently when OJ and Metformin are supplied simultaneously as opposed to when they are taken separately. Due to this reason, the simultaneous administration of OJ and Metformin is only permitted under the supervision of trained medical specialists. It is necessary to conduct additional study in order to construct OJ as a successful drug in order to gain a deeper understanding of how it functions as an antihyperlipidemic and one that treats diabetes.

6. References

1. Kumar, R., Sood, P., Nirala, R. K., Christian, A., Nyarko, R. O., Boateng, E. A., ... & Orlando, V. K. (2023). Plant & its Bioactive Components Uses in Cardio-Potential Diseases: A Sectional Study for Different Herbs. *Journal for Research in Applied Sciences and Biotechnology*, *2*(5), 61-71.
2. Saha, P., Kumar, R., Nyarko, R. O., Kahwa, I., & Owusu, P. (2021). Herbal Secondary Metabolite For Gastro-Protective Ulcer Activity With Api Structures.
3. 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.
4. Tonthubthimthong, P., Chuaprasert, S., Douglas, P., & Luewisutthichat, W. (2001). Supercritical CO2 extraction of nimbin from neem seeds–an experimental study. *Journal of Food Engineering*, *47*(4), 289-293.
5. Talwar, C., Nagar, S., Kumar, R., Scaria, J., Lal, R., & Negi, R. K. (2020). Defining the environmental adaptations of genus Devosia: insights into its expansive short peptide transport system and positively selected genes. *Scientific reports*, *10*(1), 1151.
6. Tonthubthimthong, P., Douglas, P. L., Douglas, S., Luewisutthichat, W., Teppaitoon, W., & Pengsopa, L. E. (2004). Extraction of nimbin from neem seeds using supercritical CO2 and a supercritical CO2–methanol mixture. *The Journal of supercritical fluids*, *30*(3), 287-301.
7. Zahedi, G., Elkamel, A., & Lohi, A. (2010). Genetic algorithm optimization of supercritical fluid extraction of nimbin from neem seeds. *Journal of food engineering*, *97*(2), 127-134.
8. Usman, A., Fitzsimmons-Thoss, V., & Tawfike, A. (2020). Anti-Bacterial, Anti-Oxidant and Cytotoxic Activities of Nimbin Isolated from African Azadirachta Indica Seed Oil. *Adv. J. Chem*, *2*, 81-90.
9. Zahedi, G., Elkamel, A., & Biglari, M. (2011). Optimization and sensitivity analysis of an extended distributed dynamic model of supercritical carbon dioxide extraction of nimbin from neem seeds. *Journal of Food Process Engineering*, *34*(6), 2156-2176.
10. Sarkar, L., Oko, L., Gupta, S., Bubak, A. N., Das, B., Gupta, P., ... & Sarma, J. D. (2022). Azadirachta indica A. Juss bark extract and its Nimbin isomers restrict β-coronaviral infection and replication. *Virology*, *569*, 13-28.
11. Agrawal, H., Kaul, N., Paradkar, A. R., & Mahadik, K. R. (2005). Standardization of crude extract of neem seed kernels (Azadirachta indica A. Juss) and commercial neem based formulations using HPTLC and extended length packed-columns SFC method. *Chromatographia*, *62*, 183-195.
12. Gupta, A., Naraniwal, M., & Kothari, V. (2012). Modern extraction methods for preparation of bioactive plant extracts. *International journal of applied and natural sciences*, *1*(1), 8-26.
13. Gupta, A., Naraniwal, M., & Kothari, V. (2012). Modern extraction methods for preparation of bioactive plant extracts. *International journal of applied and natural sciences*, *1*(1), 8-26.
14. Sahana, S., Kumar, R., Nag, S., Paul, R., Chatterjee, I., & Guha, N. (2020). A Review On Alzheimer Disease And Future Prospects.
15. 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.
16. Nalimu, F., Oloro, J., Kahwa, I., & Ogwang, P. E. (2021). Review on the phytochemistry and toxicological profiles of Aloe vera and Aloe ferox. *Future Journal of Pharmaceutical Sciences*, *7*, 1-21.
17. Saha, P., Nyarko, R. O., Lokare, P., Kahwa, I., Boateng, P. O., & Asum, C. (2022). Effect of Covid-19 in Management of Lung Cancer Disease: A Review. *Asian Journal of Pharmaceutical Research and Development*, *10*(3), 58-64.
18. Saha, P., Nyarko, R. O., Lokare, P., Kahwa, I., Boateng, P. O., & Asum, C. (2022). Effect of Covid-19 in Management of Lung Cancer Disease: A Review. *Asian Journal of Pharmaceutical Research and Development*, *10*(3), 58-64.
19. Kumar, R., Jangir, D. K., Verma, G., Shekhar, S., Hanpude, P., Kumar, S., ... & Kanti Maiti, T. (2017). S-nitrosylation of UCHL1 induces its structural instability and promotes α-synuclein aggregation. *Scientific reports*, *7*(1), 44558.
20. Saha, P. (2020). Evolution of tolbutamide in the treatment of diabetes mellitus. *Diabetes*, *2*(10).
21. Daharia, A., Jaiswal, V. K., Royal, K. P., Sharma, H., Joginath, A. K., Kumar, R., & Saha, P. (2022). A Comparative review on ginger and garlic with their pharmacological Action. *Asian Journal of Pharmaceutical Research and Development*, *10*(3), 65-69.

22. 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.
23. Bind, A., Das, S., Singh, V. D., Kumar, R., Chourasia, A., & Saha, P. (2020). Natural bioactives for the potential management of gastric ulceration. *Turkish Journal of Physiotherapy and Rehabilitation*, *32*(3), 221-226.
24. 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.
25. Kumar, R., & Saha, P. (2022). A review on artificial intelligence and machine learning to improve cancer management and drug discovery. *International Journal for Research in Applied Sciences and Biotechnology*, *9*(3), 149-156.
26. Kumar, R., Saha, P., Kumar, Y., Sahana, S., Dubey, A., & Prakash, O. (2020). A Review on Diabetes Mellitus: Type1 & Type2. *World Journal of Pharmacy and Pharmaceutical Sciences*, *9*(10), 838-850.
27. Kumar, R., Sood, U., Gupta, V., Singh, M., Scaria, J., & Lal, R. (2020). Recent advancements in the development of modern probiotics for restoring human gut microbiome dysbiosis. *Indian journal of microbiology*, *60*, 12-25.
28. 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
29. 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.
30. Kaur, R. P., Vasudeva, K., Kumar, R., & Munshi, A. (2018). Role of p53 gene in breast cancer: focus on mutation spectrum and therapeutic strategies. *Current pharmaceutical design*, *24*(30), 3566-3575.
31. Gérard, A., Woolfe, A., Mottet, G., Reichen, M., Castrillon, C., Menrath, V., ... & Brenan, C. (2020). High-throughput single-cell activity-based screening and sequencing of antibodies using droplet microfluidics. *Nature biotechnology*, *38*(6), 715-721.
32. Kumar, A., Uniyal, Y., & Kumar, R. (2022). Recent Advancement of Colorectal Cancer and Their Herbal Essential Oil Treatment. *Journal for Research in Applied Sciences and Biotechnology*, *1*(5), 133-144.
33. Butola, K., Bisht, V., & Kumar, R. (2023). Recent Approaches of Ocular Disease and Its Herbal Product Treatment: An Updates. *Journal for Research in Applied Sciences and Biotechnology*, *2*(2), 102-114.
34. Kumar, R. (2023). Investigation of In-Vitro Method of Antiulcer Activity. *Journal for Research in Applied Sciences and Biotechnology*, *2*(1), 264-267.
35. Biswas, K., Tarafdar, A., Kumar, R., Singhvi, N., Sharma, M., Pabbi, S., & Shukla, P. (2020). Molecular analysis of disease-responsive genes revealing the resistance potential against Fusarium wilt (Fusarium udum Butler) dependent on genotype variability in the leguminous crop pigeonpea. *Frontiers in genetics*, *11*, 559316.
36. Shekhar, S., Kumar, A., Rana, V., Kumar, R., Mittal, C., & Tariyal, K. (2023). Recent Approaches of Matrix Release Tablet in NDDS System. *Journal for Research in Applied Sciences and Biotechnology*, *2*(3), 64-71.
37. Kumar, R., Rauwel, P., Kriipsalu, M., & Rauwel, E. (2022, July). A colorimetric method of As3+ ion detection and quantification using hand-held Lovibond photometers. In *Journal of Physics: Conference Series* (Vol. 2315, No. 1, p. 012031). IOP Publishing.
38. PASWAN, S. K., DHARMENDRA AHUJA, D. L., KUMAR, S., MUZTABA, M., AHMAD, A., Selvakumar, P., ... & KUMAR, R. (2023). Volatile Alkaloids And Brain Disorder Investigation Of The Cognitive And Mood Effects Of Zingiber Officinale Essential Oil With In Vitro Properties Relevant To Central Nervous System Function. *Journal of Pharmaceutical Negative Results*, 574-589.
39. Kumar, R. S., Singh, A. P., & Singh, A. (2022). A Meta Analysis on Cardiac Vascular Disease with Obesity. *Journal for Research in Applied Sciences and Biotechnology*, *1*(3), 78-85.
40. Ghimeray, A. K., Jin, C. W., Ghimire, B. K., & Cho, D. H. (2009). Antioxidant activity and quantitative estimation of azadirachtin and nimbin in Azadirachta indica A. Juss grown in foothills of Nepal. *African Journal of Biotechnology*, *8*(13).
41. Rai, A., Punase, K. D., Mohanty, B., & Bhargava, R. (2014). Evaluation of models for supercritical fluid extraction. *International Journal of Heat and Mass Transfer*, *72*, 274-287.
42. Hatami, T., Meireles, M. A. A., & Zahedi, G. (2010). Mathematical modeling and genetic algorithm optimization of clove oil extraction with supercritical carbon dioxide. *The Journal of Supercritical Fluids*, *51*(3), 331-338.

43. Sudhakaran, G., Prathap, P., Guru, A., Rajesh, R., Sathish, S., Madhavan, T., ... & Arockiaraj, J. (2022). Anti-inflammatory role demonstrated both in vitro and in vivo models using nonsteroidal tetranortriterpenoid, Nimbin (N1) and its analogs (N2 and N3) that alleviate the domestication of alternative medicine. *Cell Biology International*, *46*(5), 771-791.
44. Danlami, J. M., Arsad, A., Ahmad Zaini, M. A., & Sulaiman, H. (2014). A comparative study of various oil extraction techniques from plants. *Reviews in Chemical Engineering*, *30*(6), 605-626.
45. Ziffer, H., Weiss, U., Narayanan, G. R., & Pachapurkar, R. V. (1966). Absolute Stereochemistry of Nimbin."Complex" Optical Rotary Dispersion of Pyronimbic Acid. *The Journal of Organic Chemistry*, *31*(8), 2691-2692.