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Antioxidant and antidiabetic activity of *Andrographis paniculata* and *Rhinacanthus nasutus* in isoniazid and rifampicin induced Wistar rats

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ABSTRACT: The present investigation aimed to identify the effects of ethanolic extract of *Andrographis paniculata* Linn. and *Rhinacanthus nasutus* Kurz. on enzymatic and non-enzymatic antioxidants on isoniazid and rifampicin induced Wistar rats. Animals were randomly divided into nine groups of 6 rats each and housed in individually ventilated cages for further experimental procedure. The levels of superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), glutathione peroxidase (GPx), glutathione-s-transfersase (GST), lipid peroxides (LPO), reduced glutathione (GSH), vitamin C (vit C) and vitamin E (vit E) and carbohydrate metabolism parameters of glucose, glycogen, glucose-6-phosphatase, glucose-6-phosphatase dehydrogenase and hexokinase are estimated at the end of the study. The present study results highlighted that the leaves extract of *A. paniculata* and *R. nasutus* have an antioxidant effect and anti-diabetic activity against the toxin treated rats.

1. INTRODUCTION

The liver plays a vital role in our body. It regulates metabolism, all biochemical pathways, detoxifications and excretion of metabolic wastes (Smuckler, 1975). It is the primary organ to receive ingested and digested nutrients from the food materials, drugs and environmental pollutants, and toxicants that enter the hepatic portal vein from the digestive system. The functions of the liver can be destructively changed due to injury resulting from exposure to various toxins (Eaton et al., 1994). The free radicals cause various disorders like diabetes, hepatitis, and cardiac arrest. The antioxidant molecules present in our body can stabilize or deactivate the free radicals before they attack cells. Humans are equipped with both enzymatic and non-enzymatic antioxidants, which work simultaneously to prevent the damage of the cells and organs from the free radical attack. These antioxidants may be endogenous or exogenously, which is supplied through foods.

The most efficient enzymatic antioxidants are superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), glutathione peroxidase (GPx) and glutathione-s-transferase (GST) (Mates et al., 1999). The non-enzymatic antioxidants include reduced glutathione (GSH), vitamins E and C (vit E and vit C), melatonin, carotenoids, flavonoids, thiol groups, including glutathione, thioredoxin etc. (Mccall et al., 2000). "Antioxidant network" involves the interaction of some antioxidants with other antioxidants to regenerate its unique properties (Sies et al., 2005). The increase of reactive oxygen species (ROS) disturbed the activities of both enzymatic and non-enzymatic antioxidants, which subsequently causes the pathophysiology of diseases. Medicinal plants are noted with rich antioxidants and are traditionally used to treat various diseases (Azaizeh et al., 2003; Manikandan et al., 2016; Sivaraj et al., 2010; Vijayakumar et al., 2018). Many plant species have potent curing properties by altering the activity of antioxidant status (Vinothkumar et al., 2010). The leaves of *Andrographis*

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paniculata Linn (Akilandeswari et al., 2019) and *Rhinacanthus nasutus* Kurz in the present study (Akilandeswari et al., 2020) have been selected to find the anti-oxidant and anti-diabetic potentials in the toxin-induced rats.

2. MATERIALS AND METHODS

2.1. Collection of plants and extract preparation

Two plants are selected for the present study, namely, *A. paniculata* and *R.nasutus.* The fresh leaves of the plants were collected from Trichy and Coimbatore**.** The plant's leaves were identified and authenticated by a Botanist, and the specimen was deposited at RAPINAT Herbarium, St. Joseph's College, Tiruchirappalli, Tamil Nadu. The voucher specimens of the plants were GA 001 and GA 002. The fresh leaves of the plant's shade dried for the study.

2.2. The ethical issue, animals, housing and experimental design

Healthy adult Wistar strain of albino rats of both sexes (150g-200g; two to three months old) was acquired from Tamil Nadu Veterinary and Animal Sciences University, Chennai, India and the animals were allowed to adapt under the laboratory conditions for five days. Animals were kept in the standard polypropylene cages lined with husk and maintained under the semi-natural conditions of 12:12-hour's light/dark cycle and temperature at 23 ± 2 ^{0}C, with 65 ± 5% humidity. All the studies were conducted according to the animal managed, and the Institutional Animal Ethical Committee approved the experimental process, Srimad Andavan College of Arts and Science**,** Tiruchirappalli, India, (Registration Number: SAC/IAEC/BC/2016-/Ph.D.-006).

Rats were randomly divided into nine groups of 6 rats each and housed in individually ventilated cages. Animals were divided into nine groups of six rats weighing 150g-200g (both sex) each. The experimental design given below has been followed for the present study. Ethanolic leaf extracts of *A. paniculata* and *R. nasutus* were freshly suspended in sterile water (300mg/kg b.w.)were administered to rats post-orally as a single dosage orally by intubation early morning for each day of the experimental period. Animal groups were categorized as control (basal diet, G1) were given saline water, isoniazid and rifampicin induced as negative control (G2), G2 supplemented with 100 mg/kg of ethanolic leaf extract of *A. paniculata* (G3) G2 supplemented with 200 mg/kg of ethanolic leaf extract of *A. paniculata* (G4), G2 supplemented with 400 mg/kg of ethanolic leaf extract of *A. paniculata* (G5), G2 supplemented with 100 mg/kg of ethanolic leaf extract of *R. nasutus* (G6), G2 supplemented with 200 mg/kg of ethanolic leaf extract of *R. nasutus* (G7), G2 supplemented with 400 mg/kg of ethanolic leaf extract of *R. nasutus* (G8) and G2 supplemented with the 25 mg/kg of silymarin (G9).

2.3. Biochemical evaluation in the serum and tissue samples

After 21 days of the study, all the animals were anaesthetized using ketamine (24 mg/kg, intramuscular injection), Furthermore, sacrificed by cervical dislocation between 8:00 am, and 9:00 am. The samples were introduced to find the following parameters. The levels of SOD, CAT, GR and GPx, GST, lipid peroxides (LPO), GSH, vitamin E and vitamin C and carbohydrate metabolizing such as glucose, glycogen, glucose-6-phosphatase, glucose-6-phosphatase dehydrogenase and hexokinase and kidney parameters such as urea, uric acid and creatinine are estimated at the end of the study. All the biochemical parameters were done using commercially available kits and were determined by a fully automated biochemical analyzer (Turbo Chem 100, CPC Diagnostics).

2.4. Statistical analysis

The statistical significance was carried out using one-way analysis of variance followed by Duncan's Multiple Range Test (SPSS® for Windows, V.17.0, Chicago, USA), and the values are expressed as mean and standard deviation. The $p < 0.05$ was statistically significant in all the tested parameters.

3. RESULT AND DISCUSSION

3.1. Enzymatic Antioxidants

Table 1 shows the antioxidant enzymes of SOD, CAT, GR, GPx and GST in the experimental groups of rats and control. In toxin treated rats, all the anti-oxidant enzymes levels were significantly ($p < 0.05$) altered when compared with the control group. After the treatment of *A. paniculata* and *R. nastus*, the levels were increased.

SOD is the primary enzyme involved in the anti-oxidant defence mechanism. SOD is a metalloprotein. SOD plays a vital role in protecting the cell from ROS (Vijayakumar et al., 2020; Yamaguchi et al., 1994). The increasing concentration of superoxide radicals may reduce the SOD level in tumour cells (Kuchi et al., 2021; Oberley & Buettner, 1979). CAT is a hemoprotein present abundantly in the body. The highest activity is noted in the liver. CAT catalyses the breakdown of H_2O_2. This H_2O_2 breaks and forms a decreasing CAT concentration, increasing the H_2O_2 level (Freeman & Crapo, 1982; Vijayakumar et al., 2020). This may prove in the present study also.

GPx is an enzyme that acts against the oxidative state imbalance by reducing the H_2O_2 and lipid hydroperoxide levels. In tumour conditions, the lipid hydroperoxide level is increased because of the decreasing concentration of GPx. GST plays a vital role in protecting tissue from the harmful effects of toxic substances and influences the lipid peroxide involved reactions. GST involves the conjugation activity towards 4-hydroxynoneal and produces the LPO (Jensen et al., 1986; Khan et al., 2016; Vijayakumar et al., 2021). The present study's findings noted that a decreasing level of GST is inversely proportional to the increasing concentration of LPO. Similar effects have been identified in *Psidium guajava* Linn. (Manikandan & Anand, 2016) and *Macrotyloma uniflorum* (Lam.) Verdc. formulation (Bharathi et al., 2018).

Table 1
Effect of *Andrographis paniculata* and *Rhinacanthus nasutus* extract on enzymatic antioxidant in the experimental animals

Groups	SOD	CAT	GR	GPx	GST
Group I	13.94 ± 1.05^{a}	39.1 ± 1.0^{a}	5135.0 ± 155.2^{a}	1285.0 ± 30.4^{a}	24550.0 ± 261.7^{a}
Group II	5.68 ± 0.63^{b}	14.2 ± 2.1b	2545.0 ± 132.5^{b}	617.0 ± 33.0^{b}	8420.0 ± 218.2^{b}
Group III	7.08 ± 0.59^{c}	25.1 ± 0.8^{c}	3250.0 ± 83.7^{c}	702.5 ± 44.2^{c}	12140.0 ± 193.8^{c}
Group IV	8.71 ± 0.52^{d}	31.9 ± 1.2^{d}	4325.0 ± 161.6^{d}	994.0 ± 18.5^{d}	17570.0 ± 166.4^{d}
Group V	13.08 ± 0.64^{a}	$37.9\pm0.5^{a,e}$	5050.0 ± 200.0^{e}	1180.0 ± 30.7^{e}	21750.0 ± 254.0^{e}
Group VI	6.50 ± 0.27^{c}	22.8 ± 0.4^{f}	3062.5 ± 150.5^{c}	685.0 ± 9.2^{c}	10850.0 ± 180.9^{c}
Group VII	7.94 ± 0.17^{c}	29.2 ± 0.7^{d}	4125.0 ± 127.0^{d}	850.0 ± 31.6^{f}	15610.0 ± 392.9^{f}
Group VIII	12.20 ± 0.53^{e}	35.8 ± 0.5^{e}	4825.0 ± 141.9^{f}	1055.0 ± 14.3^{d}	18540.0 ± 305.1^{d}
Group IX	13.89 ± 0.73^{a}	$38.3\pm0.3^{a,e}$	$5112.5\pm233.5^{a,e}$	1200.0 ± 45.2^{e}	22700.0 ± 934.9^{e}

Superoxide Dismutase (SOD; U/mg protein); Catalase (CAT; U/mg protein); Glutathione Reductase (GR; μM of GSH reduced /min/mg protein); Glutathione Peroxidase (GPx; μM of GSH oxidised/min/mg protein); Glutathione-S-Transferase (GST; μmoles of CDNB-GSH conjugate formed/min/mg protein)
Values are given in the table as means $\pm$ standard deviation for 6 rats
^{a,b,c,d,e,f} means in the same column with different superscripts differ ($p < 0.05$)

GR is an enzyme mainly involved in GSH regulation. The decreasing level of GR also reduces the GSH. This may be happened because of oxidative stress in toxin-induced rats. The reduction of GR level may induce the host's susceptibility to toxicity. In toxin-induced rats, the concentration of GR is reduced because of the induction of oxidative stress. After the treatment of *A. paniculata* and *R. nastus*, the level of GR is increased; this may be due to the reduction of oxidative stress by the action of plant extract. The previous results of Dash et al. (2007) also proved the anti-oxidative mechanisms in the herbal extract treated rats.

3.2. Non-enzymatic Antioxidants

Table 2 shows the concentrations of LPO, GSH, vit E and vit C in the experimental group of rats and control. The results indicated that the level of LPO is increased, and the GSH, vit E and vit C levels are noted to decrease in the toxin treated rats. This may prove the severity of the oxidative stress due to the administration of toxins. After treating A. paniculata and R. nastus, the levels were restored. The higher concentration of both plant extracts has higher activity when compared to the lower concentration.

The excessive concentration of superoxide and H_2O_2 due to stress increases the LPO level in toxin treated rats. The superoxide and H_2O_2 is involved in the peroxidation of membrane lipids, and it induces integrity of cellular membrane-bound enzyme activities (Kaviya et al., 2022; Tosulkao & Glinsukon, 1992). GSH is mainly involved in the cellular functions, which is involved in the H_2O_2 destruction, lipid peroxides and free radical destructions. In this study, the concentration of GSH is reduced and favours free radical productions. After the treatment of *A. paniculata* and *R. nastus* increases the concentration of GSH,it suppresses the free radical levels. Bafna and Balaraman (2005) studied that the treatment of herbomineral formulation in ulcerated rats reduces the LPO level and increases the GSH level. This may prove in the present study also.

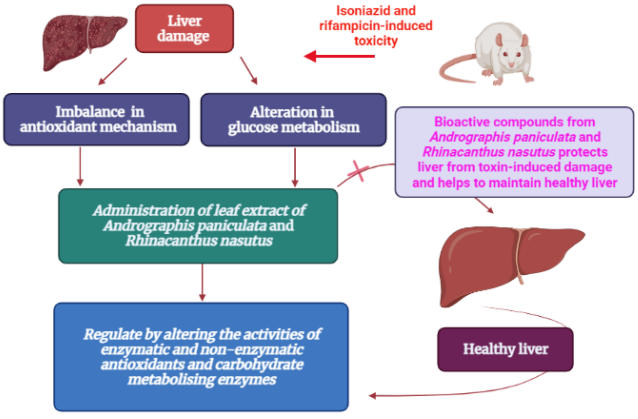

Figure 1. Schematic diagram of possible mechanisms of bioactive compounds.

Table 2
Effect of *Andrographis paniculata* and *Rhinacanthus nasutus* extract on non-enzymatic antioxidant in the experimental animals

Groups	LPO	GSH	Vit C	Vit E
Group I	66.3 ± 2.0^{a}	18.7 ± 0.8^{a}	255.0 ± 7.3^{a}	24.8 ± 0.4^{a}
Group II	141.0 ± 2.4^{b}	11.2 ± 1.2^{b}	164.0 ± 2.5^{b}	14.2 ± 0.2^{b}
Group III	114.3 ± 1.9^{c}	16.4 ± 0.2^{c}	196.3 ± 1.3^{c}	18.6 ± 0.3^{c}
Group IV	86.3 ± 2.9^{d}	17.2 ± 0.9^{c}	226.0 ± 1.9^{d}	20.5 ± 0.2^{c}
Group V	64.7 ± 1.9^{a}	18.3 ± 0.4^{a}	238.8 ± 1.9^{d}	23.4 ± 0.3^{d}
Group VI	119.3 ± 3.9^{c}	15.9 ± 1.1^{c}	180.3 ± 5.0^{e}	17.2 ± 0.3^{c}
Group VII	93.0 ± 1.8^{e}	16.9 ± 0.8^{c}	212.2 ± 3.4^{f}	19.2 ± 0.2^{c}
Group VIII	73.3 ± 2.4^{f}	17.7 ± 0.6^{c}	228.3 ± 2.2^{d}	22.1 ± 0.4^{d}
Group IX	65.3 ± 1.6^{a}	18.5 ± 0.6^{a}	232.1 ± 3.8^{d}	24.1 ± 0.2^{a}

Lipid Peroxides (LPO; nmol MDA/mg protein); Reduced Glutathione (GSH; μg/ g tissue); Vitamin C (Vit C; μg/g tissue); Vitamin E (Vit E; μg/g tissue)
Values are given in the table as means $\pm$ standard deviation for 6 rats
^{a,b,c,d,e,f} means in the same column with different superscripts differ ($p < 0.05$)

Table 3
Effect of plant extract on Glucose, Glycogen, Glucose 6 phosphatase, G-6-P Dehydrogenase and Hexokinase of experimental animals

Groups	Glucose (mg/dl)	Glycogen(mg/ g tissue)	Glucose 6 phosphatase (μmole of Pi liberated/min/mg protein	G-6-P Dehydrogenase (μmole of NADP reduced/min/mg protein)	Hexokinase(μM of Glucose utilized/min/mg protein)
Group I	127.67 ± 3.94^{a}	53.99 ± 2.73^{a}	65.28 ± 1.67^{a}	326.2 ± 7.0^{a}	132.55 ± 1.01^{a}
Group II	79.67 ± 3.79^{b}	26.09 ± 1.35^{b}	119.79 ± 1.76^{b}	197.0 ± 6.0^{b}	55.55 ± 3.35^{b}
Group III	91.00 ± 4.27^{c}	33.84 ± 2.13^{c}	100.69 ± 3.47^{c}	239.9 ± 5.2^{c}	78.65 ± 2.16^{c}
Group IV	105.17 ± 4.12^{d}	41.08 ± 2.29^{d}	78.13 ± 3.72^{d}	285.7 ± 11.1^{d}	96.25 ± 2.32^{d}
Group V	121.50 ± 3.33^{e}	$51.67\pm1.99^{a,e}$	68.06 ± 3.39^{a}	318.5 ± 4.6^{a}	$129.25\pm1.57^{a,e}$
Group VI	83.50 ± 5.10^{f}	30.23 ± 1.18^{c}	110.07 ± 1.97^{e}	221.7 ± 8.2^{e}	73.70 ± 1.84^{f}
Group VII	99.67 ± 3.49^{g}	36.68 ± 1.03^{f}	82.29 ± 2.45^{d}	261.9 ± 11.5^{f}	$91.85\pm1.32^{d,g}$
Group VIII	115.50 ± 3.00^{e}	47.02 ± 3.09^{g}	70.83 ± 4.90^{a}	303.2 ± 4.1^{g}	$127.05\pm2.21^{a,e}$
Group IX	$123.50\pm3.96^{a,e}$	$52.44\pm1.35^{a,e}$	66.32 ± 1.74^{a}	324.2 ± 3.9^{a}	$130.35\pm1.13^{a,e}$

Values are given in the table as means ± standard deviation for 6 rats
^{a,b,c,d,e,f} means in the same column with different superscripts differ ($p < 0.05$)

Table 4
Effect of plant extract on Urea, Uric Acid and Creatinine of experimental animals

Groups	Urea (mg/dl)	Uric Acid (mg/dl)	Creatinine (mg/dl)
Group I	19.39 ± 0.77^{a}	1.52 ± 0.06^{a}	0.77 ± 0.02^{a}
Group II	61.38 ± 2.07^{b}	4.48 ± 0.18^{b}	1.54 ± 0.06^{b}
Group III	44.51 ± 1.66^{c}	3.68 ± 0.07^{c}	1.24 ± 0.03^{c}
Group IV	32.44 ± 1.08^{d}	2.57 ± 0.05^{d}	1.11 ± 0.05^{d}
Group V	21.43 ± 0.95^{a}	$1.63\pm0.06^{a,e}$	0.81 ± 0.03^{a}
Group VI	49.58 ± 1.35^{e}	3.84 ± 0.05^{c}	1.35 ± 0.04^{e}
Group VII	38.18 ± 0.65^{c}	2.82 ± 0.06^{d}	1.22 ± 0.02^{c}
Group VIII	26.48 ± 1.15^{f}	1.85 ± 0.05^{f}	1.01 ± 0.03^{d}
Group IX	21.36 ± 0.60^{a}	1.59 ± 0.03^{a}	0.79 ± 0.02^{a}

Values are given in the table as means ± standard deviation for 6rats
^{a,b,c,d,e,f} means in the same column with different superscripts differ ($p < 0.05$)

The cellular membranes contain lipid-soluble non-antioxidants (vit E and vit C). Vit E is mainly involved in reducing free radicals, and vit C are concerned with recycling vit E as the free radical scavenger. In the treatment of toxins, vit E and vit C levels are decreased. In treatment with *A. paniculata* and *R. nastus* leaf extracts, the levels are increased, and these levels are nearer to the silymarin treated rats. The possible mechanism of the *A. paniculata* and *R. nastus* leaf extracts have been given in Figure 1.

3.3. Carbohydrate Metabolism

Table 3 shows the results of carbohydrate related parameters. The level of glucose, glycogen, glucose-6-phosphate dehydrogenase and hexokinase is reduced, and the level of glucose-6-phosphatase is increased in the toxin-induced rats. After the treatment of *A. paniculata*, *R. nastus* and silymarin, the levels were returned to normal.

The toxin alters the various carbohydrate metabolic processes like glycolysis, TCA cycle, and glycogenolysis in the present study. Because of mitochondrial membrane damage, the enzyme levels were altered. Anaerobic glycolysis needs more energy for their tissues survival. So it utilized more amount of glucose from the blood. Because of this, the glucose level decreases and is utilized for the glycolysis process. In toxic rats, the need for high energy the glycogen breakdown and glucose utilization is increased and decreases the glucose and glycogen level in blood.

After the treatment, the mitochondrial membranes are restored, favouring glucose production. It increases the glucose and glycogen level in rats. Among the glycolysis and gluconeogenesis enzymes, the level of glucose-6-phosphate dehydrogenase is significantly ($p < 0.05$) increased in tissues. The mitochondrial membrane damageshifts from aerobic to anaerobic glycolysis pathway. This increases the LDH and decreases the MDH activity in rats. This statement is proven in the present study also.

Hexokinase is the main compound associated with the glycolysis cycle, catalyzing the phosphorylation of glucose by ATP to glucose-6-P. It is the compound that controls glycolysis measures. The glucose 6-phosphate is an inhibitor of hexokinase, so if different pathways are moderate and if phosphofructokinase is hindered, glucose 6-phosphate will increment and restrain hexokinase level in blood. Typically, the expanding centralization of glucose-6-phosphate lessens the hexokinase level. This may also be demonstrated in the current study (Tornheim, 2018).

3.4. Kidney parameters

Table 4 shows the results of urea, uric acid and creatinine. The levels were significantly increased in the isoniazid and rifampicin induced rats compared to the control rats. The elevation of this compound is indirectly proportional to the decreasing concentration of total protein. This is due to the disruption of the structure and functional impairment of the kidney. All the three parameters levels were significantly increased in the *A. paniculata*, and *R. nastus* treated rats.

The end product of protein catabolism is urea. It is one of the essential waste products, and the kidney removes it from blood (Orth & Ritz, 1998). The end product of purine metabolism is uric acid. In our body, the waste product from muscle metabolism is creatinine. The kidney mainly discharged this. If the creatinine concentration increases, it denotesrenal dysfunction (Winnett et al., 2010).

In the present study, the treatment of *A. paniculata*, *R. nastus* and silymarin in the isoniazid and rifampicin induced hepatotoxic rats, the level of kidney parameters are returnedto normal. The increasing concentration of total protein by an anabolism also reduces the urea, uric acid and creatinine level. This activity is due to various phytoconstituents present in the extracts.

4. CONCLUSION

The present study proves the anti-oxidant and anti-diabetic efficiency of ethanolic leaf extract of *A. paniculata* and *R. nastus* in rats. This activity is due to various phytochemicals such as phenol, terpenoids, quinone and alkaloids. Further, molecular level studies are needed to find the various medicinal activities of both plants. It may be used as a drug for its various biomedical activities in the future.

5. DATA AVAILABILITY

The data set for the present study is available from the corresponding author upon request.

CONFLICTS OF INTEREST

Given his role as Associate Editor, Balamuralikrishnan Balasubramanian has not been involved and has no access to information regarding the peer review of this article. Full responsibility for the editorial process for this article was delegated to Associate Editor Gokhan Zengin. There is no conflict of interest.

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AUTHOR CONTRIBUTIONS

B.B, V.A.A. - Research concept and design; A.G., R.M., S.V., M.S. - Collection and/or assembly of data; B.B., S.V., V.A.A - Data analysis and interpretation; A.G., R.M., - Writing the article; BB, S.V., S.M., V.A.A - Critical revision of the article. All authors approved final version of the article for publication.

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