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IN-VIVOTOXICITYSTUDYANDSCREENINGOFIMMUNOMODULATORY ACTIVITY

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ABSTRACT
Traditional medicine makes extensive use of Curcuma species (family: Zingiberaceae) to address a variety of immune-related conditions. Their ethnopharmacological usage have been backed by numerous scientific investigations into their immunomodulatory effects. The article provided a critical analysis of the immunomodulatory properties of Curcuma plant different species, examined potential avenues for further study, and provided pertinent perspectives on the facilities as a potential source of novel immunomodulators to regulate. In vivo trials using the plants' crude extracts were the main focus of pharmacological investigations into their immunomodulatory effects. There was a dearth of mechanistic research into the underlying mechanisms, and most of the bioactive metabolites with immunomodulatory properties had already been identified. By the end of the 14-day study, haematological parameters had been examined. Clinical trials for the development of immunomodulatory drugs cannot be pursued without further comprehensive toxicity investigations and investigation into exploring the fundamental processes of immune-related disorders using in vivo laboratory model animals.
Keywords: *traditional medicine, immunomodulatory, bioactive metabolites, toxicity, immune-related illness.*

Introduction
Multiple studies have shown the capacity of medicinal plants to regulate immunological responses. Scientific research has demonstrated that these plants possess remarkable healing properties and can effectively treat a diverse range of human illnesses and afflictions. The immune system's intricate functioning can influence various systems in the body, including the neurological system, endocrine system, and metabolism. There has been increased interest in the immune-modulating characteristics of medicinal plants and their extracts, as well as multi-component drugs that contain active components. The primary role of the active components in these plants is to enhance and fortify the immune system (Nair A et al., 2019, Zarrin A A et al., 2021). Additional study is required to ascertain the safety and efficacy of plant products, as their usage may be subject to unique limitations. Despite these disadvantages, studies have demonstrated that medicinal plants have the potential to create novel approaches for modulating the immune system. There is an increasing acknowledgment of the potential of these plants as supplementary treatments for various ailments, including viral infections. Immunomodulation therapy refers to a therapeutic approach that involves manipulating the immune system by immunological stimulation, immune suppression, or creation of immunologic tolerance in order to regulate or change immune responses to a desired extent. A material is called the immunomodulator or medication that can modify or alter immune cell systems to produce a specific immune response by modulating the target immune systems in a dynamic manner (Spelmam K et al., 2006). The objective of the in vivo toxicity research and immunomodulatory activity screening was to analyze the safety and immune-modulating effects of the plant extracts in animal models, specifically rats, in accordance with established recommendations. The investigation aimed to determine the safe dosage ranges and evaluate any potential acute toxicity.

Materials and methods
Chemicals
The following substances were used in the experiment: Tween 80, Dexomethsone (Sigma-Aldrich), levamisole (Sigma-Aldrich), colloidal carbon ink, sodium carbonate, plethysmometer surfactant

solution, distilled water, agar, EDTA, phosphate buffered saline "(PBS, 7.4), 0.9% w/v sodium chloride solution", Wright's stain, Leishman's stain, sodium pentobarbital, EDTA blood sample tube, blood serum tube, nylon fibers, cyclophosphamide (Sigma-Aldrich), and Biochemical parameter estimation kit (Pravansha S et al., 2012).

"Sub-acute toxicity study (Repeated dose 28-day oral toxicity)"

Several administrative bodies a 28-day research on oral toxicity was done following the parameters specified in OECD 407 (2008). Fifty rats, comprising equal numbers of males and females, were divided into five groups. One group was assigned as the control; while two groups received two different dosages of Turmeric extract (EEGS) extract and two groups received two different doses of lemon peel extract (EEHS). The animals were orally given the test extract once daily for a period of 28 days. Regular daily observations were conducted on the animals to monitor mortality, changes in behavior, condition of skin and hair, respiratory patterns, health of eyes and mucous membranes, and levels of activity. The Sysmex XN1000 was used to assess the haematological parameters. In addition, the researchers evaluated the participants' food consumption and body mass (EI Kabbaouo M et al., 2017).

Results and discussion

Effectofextractsonhaematologicalparametersinsubacutetoxicitystudy

The hematological study of the extracts revealed significant alterations in the blood composition of male and female rats after a 28-day administration of the extracts, in compliance with the OECD guideline 407. The study demonstrated that administering a dose of "200 mg/kg of EEHS led to a significant ($p < 0.05$) rise in red blood cell (RBC) and white blood cell (WBC)" counts in female rats, when compared to the control group (as indicated in table 18). "A significant increase ($p < 0.05$)"in the concentration of neutrophils and the quantity of white bloodstream cells was seen in female rats given a dosage of 400 mg/kg. The haematocrit % undergoes a significant alteration when female rats are administered a dosage of 400 mg/kg of EEHS. An administration of 400 mg/kg in male rats led to a significant increase in both "red blood cell (RBC) count and white blood cell (WBC) count." No significant alterations were seen in male and female rats administered with either 20 mg/kg or 40 mg/kg doses of turmeric ethanolic extract, in comparison to the control group.

Table: 1"Haematologicalparametersoffemaleratsafter28daysofsub-acute toxicity test*"

Parameter	Control	EEGS 20 mg/kg	EEGS 40 mg/kg	EEHS 200 mg/kg	EEHS 400 mg/kg
RBC(10^6/µl)	9.16± 1.02	8.8±0.5	8.61±0.29	10.22±1.02*	8.49±0.17
WBC(10^3/µl)	11.09± 0.13	9.29± 1.4	11.57±0.94	13.67± 2.74*	14.08±1.07*
Hb(g/dl)	12.77± 1.06	11.65± 2.09	12.02±0.89	10.99± 0.91	12.49±1.58
Platelets(10^3/µl)	889.19±57.6	926.39±40.61	910.51±77.09	918.32±82.11	896 ±52.45
HCT(%)	47.66± 2.34	46.02± 1.92	45.78±0.41	46.22± 1.45	44.62±1.98*
MCV(fL)	56.85± 1.22	58.24± 0.78	56.34±1.92	55.02± 1.29	57.07±0.91
Neutrophil(%)	7.48± 0.91	7.88± 1.14	8.26±2.72	7.96± 1.25	6.94± 0.43

Lymphocyte(%)	82.02±2.05	84.41± 1.97	81.09±2.93	85.16± 3.09	86.99± 2.44*
Monocyte(%)	2.33± 0.67	2.07± 0.34	1.81±0.62	1.95± 0.46	2.42± 0.11
Eosinophil(%)	1.02± 0.45	-	0.89±0.06	0.72± 0.15	0.49± 0.05
Basophils(%)	-	0.12± 0.04	-	0.17± 0.06	-

Table: 2Haematologicalparameterofmaleratsafter28daysofsub-acute Toxicity test*

Parameter	Control	EEGS 20 mg/kg	EEGS 40 mg/kg	EEHS 200 mg/kg	EEHS 400 mg/kg
RBC(10^6/µl)	8.1±0.18	8.22± 0.72	7.89± 0.88	8.65± 0.31	9.1±0.45*
WBC(10^3/µl)	10.9± 1.78	11.09± 2.3	12.7± 1.08	11.6± 3.21	14.9± 2.12*
Hb(g/dl)	14.31± 3.1	15.41± 2.5	14.91± 1.74	14.87± 3.19	16.77± 2.33
Platelets(10^3/µl)	1008± 155.2	1019± 99.6	998.66±143.41	892.09±132.5	923.11±89.03
HCT(%)	49.68± 1.89	47.62± 0.78	50.14± 1.55	50.61± 2.39	48.03± 1.89
MCV(fL)	54.33± 0.45	57.09± 1.82*	55.62± 2.03	53.79± 1.81	56.19± 2.34
Neutrophil(%)	9.76± 1.04	8.26± 0.58	10.14± 1.8	9.04± 0.89	8.98± 0.99
Lymphocyte(%)	80.75± 3.92	81.25± 2.08	79.1± 1.56	82.13± 1.92	85.56±2.78*
Monocyte(%)	1.68± 0.07	1.83± 0.02	1.9±0.13	2.01± 0.56	1.92± 0.21
Eosinophil(%)	0.2±0.04	0.1±0.02	0.4±0.23	-	0.24± 0.07
Basophils(%)	0.2±0.05	-	0.15± 0.08	0.4±0.14	-

*"Thedataareexpressedasmean±SEM,n=5"

*"Significantdifferencecomparedtothecontrolgroup(P< 0.05)"

Conclusion

This herbal infusion of lemon and mustard has anticancer and immune-modulating effects. Its chemotherapeutic action is achieved by suppression of circulation and promotion of apoptosis. The intrinsic immune system is activated, which mediates the immune-regulating impact. This medicinal drink's health advantages are mostly attributed to the physiologically useful phytochemicals found in orange and mustard. To get a deeper comprehension of the botanical drink's systems of action while further research is required.

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