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DILUTED AND DYNAMIZED SOLUTION OF *Euphorbia tirucalli*: REVISITING. LIPID TROPISM IN CHRONIC TOXICOLOGY?

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ABSTRACT

Total extract of *Euphorbia tirucalli* (Aveloz – stem with latex) is used in ethnomedicine and by several Traditional Communities to induce tumor regression orally. However, it has toxic effects. At the clinical level, after authorization from the Research Ethics Committee at the Hahnemannian Institute of Brazil, from 1997 to 2010, complementary treatment with homeopathic medicines applicable to the reduction of clinical manifestations of the Cancer

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State was aimed at the potential reduction of inflammatory endothelial injury assessed by measuring serum C-Reactive Protein (CRP). Difficult-to-control Systemic Arterial Hypertension, major depression, obesity secondary to binge eating and eating errors, and plurimetabolic syndrome are associated with elevated serum TNF-α and CRP levels, markers of local and systemic endothelial damage. They are therefore proposed as biomarkers for monitoring the pharmacological action of ultradiluted and dynamized solutions authorized by the National Health Surveillance Agency. They are also used as a strategy in psychosocial care to promote mental health through a good sleep and wakefulness pattern. Constant oxidative stress activates protein kinase C isoforms in the cell membrane, participating as a triggering factor for prevalent clinical diseases in a society that demands lifestyle changes and social vulnerabilities. The present study was designed to evaluate the effects of high dilutions of the species collected in Seropedica/RJ/Brazil in healthy female mice for a period of 18 weeks. The ultradiluted and dynamized solution (UDS) of the 70% total ethanolic extract of aerial parts of E. tirucalli was obtained through the interaction of two processes: 1:100 dilution by weight and succussion, using 30% ethanol as solvent until the dilution of 30CH (SUD 30CH), purchased monetarily from the Professor José de Barros School Pharmacy of the Hahnemannian Institute of Brazil, only for this assay authorized by the Research Ethics Committee/UFRJ. The control solutions were composed (ethanolic HD) in the same dilutions and 10 drops diluted in drinking water were administered simultaneously orally ad libitum for chronic toxicology. SUD 30CH of the Mother Tincture (TM) of E. tirucalli did not compromise the life or development of the mice over 18 weeks (water consumption, food, weight; $p > 0.05$). There was no significant variation in liver and spleen weight, nor in serum leukocytes, but it suggested peripheral recruitment, which is the ability to increase the first barrier of nonspecific defense. It was not nephrotoxic, but it was hyperglycemic and slightly hepatotoxic. It caused specific damage to serum fats, possibly by lipid peroxidation, reducing LDL, triglycerides and phospholipids. Histopathological analysis showed that it was not toxic to lymphocytes in the splenic parenchyma. It suggested an increase in the shape and activity of germinal centers (organized and hyperstained) in the presence of a molar concentration equivalent to 10-60. Furthermore, the secretion of the cytokine Tumor Necrosis Factor-α (TNF-α) at serum level remained normal ($p> 0.05$), suggesting the absence of immunosuppressive action, an observation contrary to that described in the literature for the ponderal use of the ethanolic extract. TNF-α is a cytokine secreted by macrophages and neurons, among other cell types. Its reduction in serum levels has already been correlated with major depression, and has been investigated in other types of depression. Qualitatively, it was observed that there was a change in the behavior of healthy female Swiss mice challenged with the test solution. There was a reduction in fear of daily handling by the handler, an increase in exploratory behavior of the environment and attention. The test group was the one that had the most difficulty waking up in the morning, and curiously they began to sleep in a row and under the light (instead of nestled in the dark at the bottom of the plastic box). In our society, sleep disorders are growing at a dizzying rate, triggering Systemic Arterial Hypertension, Obesity, Depression, Fibromyalgia, among other conditions that can be included in the Cancer State. Furthermore, the difference in laboratory results for that chronic toxicology test for SUD 30CH obtained from latex trituration corroborates the theory that the active-inactive interaction should be taken into account to ensure biological responses induced by ultradiluted and dynamized solutions. Aiming to deepen the understanding of the potential mechanism of action as a “phytoadaptogen-like”, defined by the FDA for neurobehavioral tests, it is proposed to investigate SUD 30CH obtained from total aqueous extract of E. tirucalli from Seropedica, Euphorbium officinarum and Euphorbia

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resinifera associated with diluted but non-dynamized controls (hormetic, excluding nanoeffect) and dynamized solvent controls, in order to also investigate not only oxygen, but also sulfur and nitrogen way of redox potential.

Keywords: *Euphorbia tirucalli*. Chronic Toxicology. Cancer State. Systemic Arterial Hypertension. Sleep Disorders.

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INTRODUCTION

The European physician Samuel Hahnemann (1810) related the patterns of illness of vital energy (miasmas) to the organization of the biotypological constitutions of beings that are composed and evaluated through the Hippocratic temperament/humor and biotype (biochemical, endocrine and immunological profiles), a theme organized and previously discussed by professors Marcelo Pustiglione & Romeu Carillo (1994).

Homeopathy, a medical specialty since 1990, in its scope of pathophysiological reasoning regarding the onset of health conditions, has broad potential in the primary preventive epidemiological aspect when the ultradiluted and dynamized solution (SUD) used acts through biochemical pathways of elimination (especially that of sulfur) and metabolic detoxification via superoxide dismutase together with antioxidant action – both pathways were previous related to immunomodulation responses (Apolinário et al., 2000; Andrade et al., 2002 *In* Andrade et al., 2022).

Several medical articles and institutional treatises mention the use of various species of the Euphorbia genus (Trindade & Lameira, 2014). Among the species used in different pharmacotechnical preparations, the Brazilian Homeopathic Pharmacopoeia (BR, MS, ANVISA, 2011) contributed with studies on *Euphorbium officinarum* and *Euphorbia resinifera*. ABRAHCON medical article provides other examples of diluted and dynamized medications that contribute to the reduction of pain, tumor volumes and wasting syndrome used for serious patients and those beyond therapeutic possibilities. The proven pharmacological action of *Euphorbia maculata* triterpenoids is cited by the National Institute of Health (NIH).

AIMS

To revisit preliminary observations of the biological action of the ultradiluted and dynamized pharmacotechnical preparation obtained from the mother tincture (TM) of *Euphorbia tirucalli* collected in Seropédica/Rio de Janeiro to discuss a novel physiotological mechanism.

METHODOLOGY

The Case Study, a qualitative approach, is a type of research that consists of the systematic and detailed analysis of an individual or collective case, to investigate the phenomenon (object) of interest (here the sum of information for pathophysiology). It was

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initially proposed for psychotherapeutic research, but its use was expanded to several areas of knowledge, due to the important phenomenological investigative potential (Ventura, 2007).

RESULTS

This case study aimed to link the reasoning of preliminary laboratory tests carried out that led to an understanding of the best way to investigate this pharmacotechnical preparation in order to demonstrate its mechanism of chronic toxicological action.

IN VITRO ASSAYS

Denise Nagamatsu and collaborators (2024) published in vitro investigations on the cytotoxicity and selectivity of HUD 30CH from the total ethanolic extract (stem with flavonoids and latex with triterpenoids and diterpenoids) of *E. tirucalli* collected in Seropédica/RJ, a solution prepared only for these biological assays described in this article and purchased monetarily from the Professor Barros pharmacy-school (Denise 10-50, AUTIC). Subsequently, effects on apoptosis markers were also investigated: mitochondrial pathways (BAX) and the CD95 ligand and cell hyperproliferation (BCL2 pathway). The complete experiment, repeated three times, did not show antineoplastic activity either through the antigen-presenting pathway or through the mitochondrial pathway, in the concentration curve tested (25 µL, 50 µL, 100 µL, 150 µL, 200 µL).

As the BCL2 pathway was also not activated in the concentration curve tested, it was evident that the SUD 30CH tested was not capable of inducing disordered cell proliferation (therefore, it was not capable of acting at the level of different isoforms of Protein Kinase C, cell membrane signaling) for the MCF7 cell line of human breast adenocarcinoma and the Melan A cell line of normal melanocytes (Nagamatsu et al., 2024).

IN VIVO ASSAYS

The veterinarian from the central vivarium of the UFRJ Health Sciences Center Paulo Hobaica and collaborators (2020) evidenced the management effect of chronic pain (persistent pain for more than 3 months) in female Swiss mice from the vivarium, with spontaneous and multifactorial breast neoplasia, Bittner's Tumor. Based on animal behavioral, motility and mood criteria, food and water intake, weight and longevity were also evaluated. For these mice, motility and longevity were maintained since these female mice

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die in about 15 days due to hemorrhage from mammary carcinoma and the test group lived on average more than 6 months. At the behavioral level, the heightened attention and exploratory curiosity, according to the veterinarians, suggested the potential participation of a central mechanism for this HUD 30CH preparation of the total extract (Hobaica et al., 2020).

Studies have shown distinct effects on mitosis and the modulation of CD4 lymphocytes, sometimes promoting and sometimes inhibiting them, in a biphasic temporal curve (Favero et al., 1990). For the observed effect of the crude latex of *E. tirucalli*, since the ingenan ester has a skeleton similar to the cortisol molecule (Wilson & Huffman, 1976) and the tiglian ester has a skeleton similar to prostaglandins, the presence of membrane receptors for prostaglandins, which are modulators of cell division, was questioned (Mosior & Newton, 1995).

Due to the lack of information on chronic and therapeutic toxicological tests in animals with *E. tirucalli* MT and respective SUD (Gomes, 2002), although both have been popularly used for decades without reports of acute intoxication and poisoning (Varricchio, 2008), in search of understanding the mechanism of action involved, it was decided to analyze groups of 5 healthy Swiss mice, preliminarily. They were subjected to oral use *ad libitum* with 10 drops of HUD 30CH of *E. tirucalli* MT, collected in Seropédica, west zone of Rio de Janeiro, according to popular use in this state of the federation. In addition to the 70% ethanol control, the SUD 30CH control of the 30% ethanol solvent was used, both prepared by the IHB School Pharmacy, purchased for this scientific investigation, used for the determined period of 18 weeks. Distilled water was provided by the Laboratory of Immunoparasitology and Toxicological Analysis/FF/CCS/UFRJ. Test carried out after authorization from the University Council for Ethics in Animal Research (Gomes et al., 2024).

There are no published chronic toxicology tests in mice for the high ultradiluted and dynamized (HUD) preparation MT of *E. tirucalli*, according to ANVISA standards, to be compared in discussion. The expected toxicity was not exhibited, as recommended by the classical literature (Bosch, 2004), suggesting that the pharmacotechnical process of ultradilution and succussion by the classical Hahnemannian method of multiple vials participated in this biological model as hypothesized by Gomes (2002), and in agreement with the theoretical body proposed by Samuel Hahnemann's Organon of the Healing Art (Gomes et al., 2024).

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For serum analysis, the blood pool was collected from each group, and the chronic toxicological effect of the test solution (High Ultra Dilution Sucussion - HUD) on peripheral blood and serum biochemistry, liver and spleen weight, histopathological analysis of the spleen were analyzed. In addition to neurobehavioral and developmental biological responses (Gomes et al., 2024).

The analysis did not show statistically significant variations in the mean absolute weight values of the liver and spleen of the test group compared to the control groups (P> 0.05). The literature points to the potential risk of long-term use of *E. tirucalli* regarding the potential risk of lymphocytic transformation discussed by Bosch (2004). For this reason, in addition to analyzing the slides to verify the count, variation in cell type and shape of the leukocytes, histopathological analysis of the spleen was performed using HE staining of the germinal centers. There were no statistically significant variations in the absolute and percentage values in the peripheral blood for HUD 30CH of *E. tirucalli* (P> 0,05). However, there was a tendency for a relative increase in the number of lymphocytes, with a reduction in neutrophils and monocytes in relation to the control group, evidence that suggested the possibility of peripheral recruitment of already formed cells (Gomes et al., 2024).

The histopathological analysis of the toxicological effect of the test solution (HUD) on the splenic parenchyma showed that the control group that ingested distilled water had organized germinal centers with very purple lymphocytes, fixing the dye, thus demonstrating that they maintained their activity. The group administered with HUD 30CH of 30% ethanol remained organized, but also reduced in number and distribution in quantity, not so increased, with lymphocytes still active. The group administered with HUD 30CH of TM of *E. tirucalli* collected in Seropedica remained with organized germinal centers, with an increase in their size, associated with an increase in the size of lymphocytes in areas close to vessels, suggesting recruitment to the periphery. They were active and functioning (Gomes et al., 2024).

HUD 30CH of the total ethanolic extract (stem with latex) of *E. tirucalli,* indeed, was able to reduce VLDL, triglycerides and phospholipids compared to controls, suggesting the ability to reduce oxidative stress via superoxidodismutase. The literature shows that total extracts of *E. tirucalli* are capable of triggering lipid peroxidation in cell membranes, as well as crude latex (Datta et al., 1999 *In* Gomes et al., 2024), results shown in Table 1:

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Table 1: Variation of the lipid profile as a marker of oxidative stress in healthy female mice under oral administration *ad libitum* for 18 weeks of HUD 30CH of *E. tirucalli* 30% of Seropédica. ND: Not measured.

Biochemical	Reference	DW	ETOH 70%	HUD 30CH ETOH 30%	HUD 30CH TM *E. tirucalli*
Tot Lip	400800	568	ND	459	451
Cholesterol	< 200	115	ND	101	102
HDL-Col	> 45	69	ND	63	69
LDL-Col	< 100	5	ND	19	17
VLDL-C	< 30	27	ND	19	16
Triglic	< 150	137	ND	94	81
Phosfolip	125 - 250	94	91	82	70

Reference Values are for humans. Source: GOMES et al. (2024).

In relation to the control group that ingested distilled water, the ethanol controls were hyperglycemic, being superior to the hyperglycemia evoked by HUD 30CH of *E. tirucalli*. In fact, it suggests that the ultradilution and dynamization process was able to attenuate the potential toxicity (Gomes et al., 2024).

No toxic effect was detected on protein metabolism or glomerular filtration, unlike that described by Datta et al. (1999), who considered total extracts nephrotoxic and cardiotoxic due to direct injury, since reactive oxygen and nitrogen species attack proteins and DNA. The maintenance of normal urea levels also adds to the observation that liver injury was mild, due to the probable reduction in the damaging potential resulting from the ultradilution and succussion process or due to the edaphoclimatic conditions of the plant collected in Seropédica, which may have imprinted specific characteristics of relative seasonal concentrations of plant chemical components in the TM (Gomes et al., 2024).

It is noteworthy that the enzyme glutamic pyruvic transaminase/TGP (alanine aminotransferase/ALT), a specific marker of liver injury due to hepatocyte lysis in the face of stress agents, remained normal in all groups, including the group administered the test solution (Gomes et al., 2024).

However, glutamic-oxaloacetic transaminase/SGOT (or aspartate aminotransferase/AST) increased 4- to 6-fold, both for the control groups and for the test solution. It is known that SGOT is not a specific marker for liver injury and is commonly used as a marker of tissue ischemia in various tissues of the body. Therefore, its elevation associated with normal SGPT, urea and creatinine, leads us to think about the occurrence of lipid peroxidation with endothelial injury and reflex vasoconstriction. There were no

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morphological manifestations at the macroscopic level compatible with ischemia in other tissues (Gomes et al., 2024).

It suggested a vasoconstrictor effect, leading to hypoxia at the local tissue level, a fact that immediately activates the secretion of phosphofructokinase 1, the main enzyme that participates in glycolysis, which could explain the hyperglycemic effect previously observed, already reported in *in vitro* tests with the preparation of HUD from latex grinding (Aquino et al., 2008). It did not suggest the installation of pancreatic injury since the animals remained well, active, without vomiting, diarrhea, or abdominal contortions (Gomes et al., 2024).

The induction of cytokine secretion in the serum of these animals was investigated. For the group of healthy Swiss mice challenged by the ingestion of HUD 30CH of TM of *E. tirucalli* from Seropedica after ad libitum ingestion for 18 weeks, in their dosages in the lymphocyte supernatants, a tendency for the TNF-α response to maintain its normal production was detected in relation to the control groups. And in the stage of the assay in which they were stimulated with Concanavalin A and SUD 30CH of *E. tirucalli*, TNF-α suffered non-significant inhibition of its production (Santa Clara Jr. In Gomes et al., 2024).

Regarding the effect of HUD 30CH of aerial part of *E. tirucalli* 30% of Seropedica on the development and behavior of healthy female Swiss mice, in relation to the control groups for the mean values calculated with their respective standard deviations, there was no statistically significant variation for motility ($p > 0.05$). Regarding food consumption, in the thirteenth and eighteenth weeks the group that ingested HUD 30CH solution-test, in its mean with standard deviation, ingested more food ($p < 0,05$) suggesting an effect on hunger related to the time of exposure to the test solution (Nagamatsu et al., 2024).

For water consumption, in the fourth week the group administered the test solution ingested significantly more water. In the eighth, twelfth, thirteenth, sixteenth and eighteenth weeks, once again, the group that ingested HUD 30CH of ethanolic extract of *E. tirucalli* obtained a significant water consumption in relation to the three controls, suggesting that the effect observed at the end of 18 weeks was not dose-dependent but was time-dependent (Nagamatsu et al., 2024).

The lower weight gain compared to controls in the fifth week appeared to be isolated and has no explanation. Although not significant, there was a tendency for weight gain in the last weeks for the group that ingested HUD 30CH from the ethanolic extract of *E.*

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tirucalli. It is noteworthy that no edema was observed, nor was there any reduction or variation in gait and motility (Nagamatsu et al., 2024).

Regarding the handling of the animals, a behavioral effect of interest was observed, with a reduction in fear and inhibition. There was a change in habits, with them sleeping in a row and in the light, in addition to taking longer to wake up in the morning compared to the control groups, suggesting deep sleep. These qualitative observations may guide future research, considering a neuroimmunomodulatory effect through a central pathway that affects the metabolic pathway through thyroid hormones (Nagamatsu et al., 2024).

Therefore, in our tests, the assessment of weight and motility also showed the absence of protein degradation due to preserved muscle mass, hair (faneri) in good condition, shiny and well distributed throughout the body. Normal attention and exploratory activity showed preserved neurological functions, observations that in the absence of obesity, suggested the participation of thyroid hormones.

DISCUSSION

Given these preliminary results, it can be thought that HUD 30CH from *E. tirucalli* was able to reduce oxidative stress at the hepatic and renal cellular level due to the presence of polyphenols from the stem, suggesting the possibility of a non-harmful or even protective effect of this HUD obtained from TM (Gomes et al., 2024).

The clinical effects secondary to the reduction in serum phospholipids observed in the healthy group that ingested HUD 30CH from *E. tirucalli* are well described in the literature. This may trigger cellular membrane disorders and, consequently, hematological repercussions such as hemolysis, leukopenia, and thrombocytopenia (already observed in other test groups of ponderal use, which presented hemolysis - Varricchio, 2008), in addition to neurological repercussions such as peripheral paralysis and even induce mitochondrial uncoupling disorders such as abrupt cessation of the respiratory chain and death, as described by Liliane Bentancur-Galves et al. (2002; 2003 *In* Gomes et al., 2024).

Could SUD 30CH from *E. tirucalli* then minimize these clinical manifestations in mice with diseases caused by these same mechanisms of action? Through this lipid peroxidation pathway in VLDL and LDL, could it reduce the extent of plaques and endothelial injury? Would it reduce inflammation? Would it reduce triglycerides and increase phospholipids in diseases that modify them seriously? Through reflex vasoconstriction triggered by

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endothelial aggression, could it act on bleeding lesions such as carcinomas, thus explaining the result observed by Hobaica et al. (2020)?

There is a membrane receptor for mediating HDL cholesterol, promoting intracellular efflux of cholesterol in healthy cells, being expressed in the liver, adrenal glands, ovaries and testes. It is an anti-atherogenic lipoprotein, apolipoprotein B100, thus redistributing free cholesterol (Wilson et al., 1998). Could it bind to it? Is the active extrusion of cytoplasmic cholesterol in normal cells (similar to a pumping for cleaning) also related to signaling promoted by different isoforms of protein kinase C (PKC) turned on or off?

In other words, the lower the cholesterol efflux (lower output), the more PKCα will act as a tumor promoter, while the higher the cholesterol efflux (higher output), the greater the antitumor activity, this time through signaling that inhibits the cell cycle, via the PKCδ pathway. Multidrug-resistant tumor cells often have impaired efflux/extrusion mechanism (Koivunen et al., 2005). In fact, Varricchio et al. (2008a) verified *in vitro* cytotoxic activity with cell cycle blockade of *E. tirucalli* weight preparations in multidrug-resistant murine melanoma cell line B16F10. Could HUD 30CH modulate PKCδ? Could this be one of the mechanisms that explains the reversal of bone metastases?

In vivo, for the observed hyperglycemic action, steroidal stimuli should be investigated due to the presence of diterpenoids whose chemical structures are similar to plasma cortisol and may increase it (Wilson & Huffman, 1976). It may also lead to increased glucagon secretion, activate the thyroid, damage the islets of Langhans by vasoconstriction or, for this reason, activate the metabolism of phosphofructokinase 1 (Williams & Wilson, 1998; Aquino et al., 2008). Varricchio et al. (2008a) found an increase in serum free T4 with the use of raw latex *ad libitum* (Gomes et al., 2024).

SUD 30CH of TM of *E. tirucalli* suggested that it could induce selective oxidative stress, directed only to lipid metabolism in these healthy animals, converging with that described for the latex of the species by Datta et al. (1999). The reduction of phospholipids seems to have been a consequence of lipid peroxidation of the cell membrane of hepatocytes, which act as markers of oxidative stress at the biochemical level. The elevation of only TGO and not of TGP suggested vasoconstriction with tissue injury, also described by the authors (Varricchio, 2008).

Macrophages and muscle cells are capable of releasing oxidized LDL, which is cytotoxic, resulting in endothelial lipid peroxidation. LDL activates the process of atherogenesis and serves as a chemotactic factor for circulating monocytes/macrophages,

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resulting in adaptive immunogenic activity, since physiological oxidative stress can evoke the differentiation of monocytes into macrophages, activating, in turn, the process of phagocytosis, mechanisms described for phytoadaptogenic extract (Panossian et al., 1997; Droge, 2000). Could HUD 30CH from TM of *E. tirucalli* exert an “adaptogenic-like” action?

The accumulation of reactive species inserts the atherogenesis process as part of the development mechanism of a series of chronic degenerative diseases of epidemiological importance, such as neoplasias, AIDS, leprosy, tuberculosis, autoimmune diseases, among others. The presence of oxidized LDL induces the endothelium and smooth muscle cells to produce monocyte chemotactic protein 1 to recruit them early to the sites of lesions in progress. Several mitogens are specific chemoattractants for endothelial cells, such as platelet-derived growth factor, basic fibroblast growth factor, insulin-like growth factor, interleukin 1, tumor necrosis factor α, and transforming growth factor β. Inflammatory cytokines include: Interleukin 1 (IL-1), Interferon gamma, Interleukin 2, Colony stimulating factors, Tissue necrosis factor α (Gomes et al., 2024).

Santa Clara Jr (2008) investigated the induction of cytokine secretion in the serum of animals tested. For the group of healthy Swiss mice challenged by the ingestion of HUD 30CH of TM of *E. tirucalli* from Seropedica after ad libitum ingestion for 18 weeks, in the lymphocyte supernatants, a tendency for the TNF-α response to maintain its normal production was detected in relation to the control groups. However, in the stage of the assay in which they were stimulated with Concanavalin A and HUD 30CH of *E. tirucalli*, TNF-α suffered non-significant inhibition of its production ($p > 0.05$) with concentrations below the controls (Gomes et al., 2024).

It was then suggested that the HUD 30CH of the TM of *E. tirucalli* from Seropédica could be capable of evoking mechanisms of action different from those observed for the ponderal dosage of the TM of *E. tirucalli* from the IPPN/UFRJ garden also tested by him, since the flavonoids and tannins present in the stem induced cytotoxic activity, via macrophage cytokine signaling (Gomes et al., 2024).

Tumor Necrosis Factor Alpha (TNF-α) corresponds to a group of cytokines capable of causing apoptosis in tumor cells and that have a wide range of pro-inflammatory actions in normal cells, being secreted mainly by macrophages. Its direct toxicity is due to being a substance identical to cachexin, a serum mediator implicated in wasting syndromes, present in parasitic diseases and active neoplasias. TNF are glycoproteins, not

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immunoglobulins, released by living host cells that act non-enzymatically, regulating several cellular functions (Santa Clara Jr., 2008 In Gomes et al., 2024).

TNFs are produced by T lymphocytes, mast cells, natural killer (NK) cells, endothelial cells, Langerhans cells, astrocytes, smooth muscle cells, and human fetal Kupffer cells. The main physiological effect of TNF-α is to promote the immune and inflammatory response through the recruitment and activation of neutrophils and monocytes to the site of infection. The recruitment of leukocytes and their cellular differentials in the periphery observed may be explained by modulation via TNF-α (Gomes et al., 2024).

TNF-α, when released in low concentrations, acts on endothelial cells, promoting vasodilation and stimulating chemokines. In the hypothalamus, it acts as an endogenous pyrogen, while in the liver it stimulates the production of proteins from the acute phase of the inflammatory process and fibrinogen, leading to changes in the coagulation cascade with an increased risk of disseminated intravascular coagulation (Santa Clara Jr., 2008 In Gomes et al., 2024).

When TNF-α is present in high concentrations, it can increase plasma insulin concentrations and cause abnormalities in the metabolism of steroid and growth hormones. It is cytotoxic to pancreatic β cells, thus playing a role in the pathogenesis of type 1 diabetes mellitus. It triggers vasoconstriction and is involved in the association of Systemic Arterial Hypertension and dyslipidemia with obesity. It can stimulate lipolysis and inhibit lipoprotein lipase, increasing free fatty acids in the plasma, causing insulin resistance (Santa Clara Jr., 2008 In Gomes et al., 2024).

It also acts in the extrinsic pathway of apoptosis and as a regulatory element of the immune system. The CD95 receptor and ligand play an important role in apoptosis during the death of mature T cells at the end of the immune response and in the death of virus-infected cells. However, in this toxicological assay there was no reduction in TNF-α compared to the control groups, therefore, preliminarily HUD 30CH of TM of *E. tirucalli* from Seropedica was not immunosuppressive (Santa Clara Jr., 2008).

These results in chronic toxicology are different from those observed by Salah-Zayed and collaborators (1998) for the toxicology of *E. peplus* and *E. tirucalli* collected in an Arab country, when marked weight loss associated with generalized edema was observed, compatible with hypoproteinemia due to established liver and kidney failure, followed by death. In the present experiment, no edema, vomiting, or diarrhea were observed (Nagamatsu et al., 2024).

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The group that used HUD 30CH of *E. tirucalli*, significantly exceeded the water consumption in relation to its control in the fourth, eighth and eighteenth weeks ($P < 0,05$), similar to that observed by Salah-Zayed et al. (1998). Therefore, these results suggest that these are the periods of onset and progression of lesions (Evans & Soper, 1978; Furstenberger & Hecker, 1986) of a metabolic syndrome and Diabetes Mellitus.

The stimulation of the pituitary thyrotropic releasing factor (TRH) by phorbol esters was recorded for the genus Euphorbia by Salah-Zayed et al. (1998 b). The neuroendocrine evaluation may contribute to the understanding of the development of mice, particularly of the group that used HUD 30CH of *E. tirucalli*, since qualitatively an increase in the level of attention and speed of responses had already been observed, with adaptation of responses to the proposed activities, such as exploratory activity and problem solving, such as overcoming obstacles in a maze (recorded on video by Gomes, Hobaica, Varricchio, Pyrrho, 2007 In Varricchio, 2008).

This observation was corroborated in chronic toxicology tests with TM prepared from the plant individual located in the IPPN/UFRJ garden, when an increase in free tetraiodothyronine (free T4) was evidenced, with a decrease in TSH and normal triiodothyronine (T3) in relation to the control groups. As proposed by Panossian and collaborators (1997), this laboratory analysis led us to question the immunomodulatory and adaptogenic metabolic effect, occurring via modulation of the thyroid gland by terpenoids that constitute plant chemical production (Varricchio, 2008).

In reasoning focused on homeopathic pathophysiology and semiology, SUD 30CH of TM of *E. tirucalli* from Seropedica suggested that it presents an antigen-presenting effect in the peripheral circulation, recruiting already mature leukocytes, appearing to exert an exonerative character similar to the pathophysiology of the sulfuric action route (Apolinário et al., 2000). It may possibly exert detoxifying activity, through the detoxification mechanism by the sulfur-methionine pathway and the glutathione peroxidase pathway (Varricchio et al., 2000 In Gomes, 2000; Varricchio, 2008 In Gomes et al., 2024).

Furthermore, during the metabolism of methionine (Met) to cysteine (Cys), homocysteine (Hcy), a sulfur-containing amino acid, is formed. Hyperhomocysteinemia (HHcy), i.e., increased circulating levels of Hcy, is generally recognized as an independent risk factor for peripheral atherosclerosis. Altered cellular export mechanisms increase Hcy levels (Kumar et al., 2017 *In* Gomes et al., 2024).

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HHcy stimulates the expression of monocyte chemoattractant protein 1 (MCP-1), vascular cell adhesion molecule 1 (VCAM-1) and E-selectin. This leads to increased adhesion of monocytes to the arterial endothelium, inflammatory response and may significantly contribute to the development of atherosclerosis, facilitating the infiltration of monocytes/macrophages into the arterial wall and the triggering of Systemic Arterial Hypertension (Kumar et al., 2017 *In* Gomes et al., 2024).

Homocysteine (Hcy) damages arterial cells and tissues, triggering the release of cytokines, cyclins, and other mediators of inflammation and cell division. In addition, it affects cellular respiration, leading to the oxidation of low-density lipoproteins (LDL) and other plaque constituents. Stamler and colleagues reported that Hcy also antagonizes the vasodilatory properties of nitric oxide (NO), forming S-nitrosohomocysteine, leading to endothelial dysfunction, a precursor to atherogenesis (Kumar et al., 2017 In Gomes et al., 2024).

There is evidence that hydrogen sulfide (H2S) production from vascular tissues is increased by nitric oxide (NO). H2S induces long-term potentiation of the hippocampus, brain development, and facilitates blood pressure regulation, relaxes smooth muscle cells to maintain blood pressure levels, and decreases neuronal excitability (Kumar et al., 2017). This last mechanism could also help explain why the test group slept longer and more deeply (Gomes et al., 2024). It will need to be investigated.

Endothelial cells produce and release H2S in a Ca2+-dependent manner after neurohumoral stimulation and evoke hyperpolarization and relaxation of vascular smooth muscle cells, activating KATP channels, leading to vasodilation and decreased blood pressure with the participation of the calcium-calmodulin complex activating other pathways (Kumar et al., 2017 *In* Gomes et al., 2024).

According to the literature, there is an association between hyperhomocysteinemia (HHcy) and vascular disease, hypothyroidism, insulin resistance, osteoporosis, cancer, gastrointestinal disorders, among others. HHcy causes endothelial dysfunction and has been attributed to impaired NO bioavailability. In cancer patients, elevated levels of Hcy may be caused by the rapid division of tumor cells, thus becoming a potential tumor biomarker. It also adversely affects the intestinal vasculature, resulting in a condition such as chronic inflammatory bowel disease (Kumar et al., 2017), and may become a good model for studying this period of neoplastic transformation in the intestinal region, known as cancerinism, which currently has virtually no therapeutic resources (Gomes et al., 2024).

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It is worth noting that the HUD 30CH-test did not induce tumor promotion in the healthy group tested. In fact, it did not develop macroscopic lesions in the other devices and systems. Assays with plasma, serum or intestinal and liver tissues can estimate the amount of Hcy and glutathione, when analyzed by High Performance Liquid Chromatography/HPLC (Kumar et al., 2017) in addition to histopathological analysis (Gomes et al., 2024).

This information will be relevant for future trials, since the chronic toxicological effect observed for SUD 30CH of TM from *E. tirucalli* collected in Seropedica preliminarily suggested a different route from that observed for the ponderal ethanol extract, which evoked reactive oxygen species. SUD 30CH of TM suggested a route of action via the sulfur pathway, a mechanism previously proposed by a literature review (Apolinario et al., 2000) and via the nitrogen pathway, as previously proposed by Varricchio (2008).

In a brief physiopathological review, physician Leon Vannier (1931) proposed the existence of a temporary state of imbalance between cellular functions and communications, according to genetic inheritance (miasma or the inherited pattern of illness and the constitution of the semiological biotypology) and the type of exposure. A clinical syndrome that would precede the outbreak of diseases expressed according to individual characteristics (sensitivity, susceptibility/genetic inheritance). For example: Cancer in patients with a previous pattern of proliferative diseases (Sycosis); self-aggressive diseases in patients with a pattern of destruction (Syphyllis); Gout in patients with a metabolic pattern of degeneration (Psora – Varricchio, 2010).

Vannier (1931) related acute stress of high intensity or low intensity, but persistent, emotional or physical (trauma, injuries, surgical trauma), generating “nervous” (local) signaling, as a triggering factor for diseases. Complaints similar to those of the Tuberculosis pattern, whose distress would overload the activity of the thyroid and adrenal glands, would reduce the assimilation of minerals (demineralization state of Tuberculinism), and due to its lack of diagnostic identification would lead to the onset of the clinical syndrome called Cancerous State (Vannier, 1931) which, in turn, if not identified, the loss of dynamic balance would generate deviation of signaling routes on the surface of the cell membrane (activating different signaling isoforms) and, in this way, could lead to the outbreak of diseases related to any of the miasmas.

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This cancerinic state (Vanier, 1931) would be progressively installed, until reaching a state of anergy and extreme sensitivity to climatic variations in environmental conditions as shown in Table 2:

Table 2: Symptoms and signs common to the Cancerous State.

Constipation x Diarrhea;
Hardening and swelling;
Skin-trophic disorders, excessive sweating, glandular imbalance;
Myalgias, arthralgias, undetermined and recurrent bone pain;
Restlessness, anguish, conflict, distrust;
Slowness, negligence, fatigue;
Weight loss, exhaustion;
Changes in humidity, temperature, atmospheric pressure.

Source: Vannier (1931).

The French school of Homeopathy brought the concept of cancerous state (Vannier, 1931) methodologically investigated and discussed over the years (Cruz Filho et al., 2023). Therefore, the triggering and quantity of symptoms in distinct systems and in distinct temporal order due to the progressive involvement of defense responses suggests the participation of a chronic inflammatory mechanism through endothelial participation via local mechanisms and cell membrane signaling. The variation of the isoforms of the Protein Kinase C (PKC) pathway in nature sometimes turns on and off the signaling for the progression of cancer, mental illnesses, immune defense mechanisms, among others (Koivunen, 2005).

By definition, homeopathy aims at a rapid, gentle and lasting response of the host, through secondary stimulation of the host's vital energy, by increasing the metabolism and exoneration of toxic elements, associated with the subjective sensation of well-being (Hahnemann, 1810 *In* Pustiglione & Carillo, 1994). In convergence, these criteria are similar to those recommended by the Food & Drug Administration (FDA) for a phyto-adaptogenic extract (Wagner et al., 1994).

According to the FDA (1998), the criteria for classifying a phytotherapeutic extract as a phytoadaptogen are: to evoke adaptation and response quickly, smoothly and accompanied by well-being in the host under stress or under any type of threat, while still being harmless to the host or to the healthy experimenter. Phytoadaptogens represent those groups of active substances, commonly originating from the special metabolism of plants, which continue to function in synergy after obtaining the plant extract and increase the adaptive metabolic and immunological responses of living beings as a whole, in the face of various distress conditions (Wagner et al., 1994; Panossian et al., 1999).

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The use of phytoadaptogens began in the post-war period to reduce distress caused by post-war trauma (which can be called post-traumatic stress), hunger, exposure to extreme temperature variations, and related infectious diseases. This range of action is due to their neuroimmunomodulation capacity, providing the rescue of the workforce for the reconstruction of life in these European countries (Panossian et al., 1999). Thus, it was theoretically understood that certain ultra-diluted and dynamized extracts could have a pharmacological mechanism in the regulation of homeostasis (Bellavite & Signorini, 1997; Gomes, 2002; Kuster et al., 2002), similar to phytoadaptogens, and can thus be called “adaptogen-like” (Varricchio, 2008).

Clinical evaluation is performed through anamnesis, physical examination, and homeopathic semiological and pathophysiological classification. At a complementary level, at least, serum C-Reactive Protein (a marker of endothelial inflammation) and specific tumor markers of neoplasia are measured, which serve both to monitor the progression and prognosis of the disease and to mitigate the cancerous state (called “drainage”), with a view to complementing specific oncological treatment, with the aim of making the endothelium less inflamed and reactive, seeking to reduce the risk of new signals or reactivation of those that trigger cell proliferation, leading to recurrence of the underlying disease (Varricchio, 2008).

Thus, the reasoning from the clinical-pathophysiological level was extended to the cellular level, with the monitoring of the expected reduction in endothelial oxidative stress existing in the Clinical Syndrome of the Cancerinic State (Varricchio, 2010), at an outpatient level verified by regular dosage of serum C-Reactive Protein. The graph generated by the monitoring should be correlated to the constitution of each patient over a year, as a minimum time, if possible. Also related to the miasma (reactive pattern of illness of each patient), Hippocratic temperament, clinical and laboratory findings pertinent to each case and the domains of a validated quality of life protocol, configuring a case series study authorized by the Medical Ethics Committee (Andrade et al., 2002 In Andrade et al., 2022).

There are empirical reports of reduction of tumor activity markers such as PSA, as well as CEA and CA 125 (Varricchio, 2008). However, the emphasis of the reports of those who use it is on the improvement of quality of life, with the return of hunger and appetite, thirst, improved sleep, increased muscle tone and strength, stabilization of mood, and interest in life, as if it acted as a remineralizing tonic with systemic

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psychoneuroimmunoendocrine action (as a “simile phyto-adaptogen” - Wagner et al., 1994 *In* Varricchio, 2008), similar to what was preliminarily verified in these trials, revisited here.

In vulnerable patients, atherosclerosis develops through the influence of conditions that traumatize the endothelium, such as aging, Systemic Arterial Hypertension, hypercholesterolemia, diabetes, smoking, and obesity itself. These factors damage the endothelium and stimulate an inflammatory/proliferative reaction in the vascular wall. This reaction increases the secretion of primary pro-inflammatory cytokines, such as interleukin (IL)-1 and tumor necrosis factor-alpha (TNF-α - Reilly et al., 2007 *In* Gomes et al., 2024).

In the process of differentiation of preadipocytes into mature adipocytes, they acquire the capacity to produce hundreds of proteins: enzymes, cytokines, growth factors and hormones involved in various metabolic events. Components involved in adipogenesis include lipoprotein lipase, angiotensinogen, adipsin, adiponectin, IL-6, prostaglandins, TNF-alpha and nitric oxide. These molecules have a modulating action on lipid deposits and body fat distribution (Reilly et al., 2007 *In* Gomes et al., 2024).

Adipokines include: TNF-alpha, IL-6, leptin, plasminogen activator inhibitor (PAI)-1, angiotensinogen, resistin and C-reactive protein (CRP). Some have protective action against vascular inflammation and insulin resistance, among which are adiponectin and nitric oxide (Gomes et al., 2010 *In* Gomes et al., 2024).

C-reactive protein (CRP) is an acute phase protein synthesized by the liver and regulated by circulating levels of IL-6. IL-1 and TNF-alpha can also induce messenger RNA expression for the production of CRP itself. Recently, high plasma CRP levels have been considered as independent predictors of coronary artery disease. While low CRP levels have been correlated with better outcomes in Major Depression. Circulating plasma CRP levels are high in obese individuals and are directly related to the amount of body fat, insulin resistance, metabolic syndrome and diabetes mellitus (Reilly et al., 2007 *In* Gomes et al., 2024).

CRP is not a mere marker of inflammatory activity: it directly participates in the process of atherogenesis and modulates endothelial function. It also induces the expression of several molecules (ICAM-1, VCAM-1, MCP-1 and selectins). It acts as a regulator of nitric oxide production in the endothelium and coordinates the production and secretion of several cytokines, increasing the proinflammatory activity of several adipokines that play an important role in this process, especially in endothelial dysfunction. Therefore, there are several possible therapeutic implications of combating leptin resistance, since this

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condition appears to be associated with several risk factors for vascular disease. Cytokine modulation occurs with the use of phytoadaptogen-like extracts (Serrano Jr. et al., 2010 *In* Gomes et al., 2024).

The number of symptoms in different systems and in different temporal order, due to the progressive involvement of defense responses, suggests the participation of a chronic inflammatory mechanism with endothelial participation, via local mechanisms and cell membrane signaling for the progression of diseases, such as cancer and mental illnesses (Koivunen, 2005). Based on the anamnesis and clinical examination, it was found that, retrospectively, 36% of the patients had developed the Cancerinic State Syndrome on average three years before the onset of the malignant neoplasm. This state wasn't identified to be mitigated its progression (Varricchio, 2010).

Regarding Systemic Arterial Hypertension (SAH) and Cancer, the literature shows more the effects of chemotherapy and radiotherapy on cancer patients (Souza et al., 2014). In this sense, the probable mechanisms of established and difficult-to-control hypertension in the cancer state, based on these preliminary tests described here, could be hypothesized according to the Law of Similarity and explained according to the concepts of metabolic biochemistry. It thus becomes possible to investigate such mechanisms of recurrent and difficult-to-control Systemic Arterial Hypertension in these patients.

The reduction or poor quality of phase 3 sleep is accompanied by an increase in cortisol. Hypercortisolism is associated with systemic inflammation and diseases associated with neuroinflammation due to the accumulation of toxic substances that are not removed by the glymphatic system during sleep, and can lead to migraines, decreased pain threshold, cognitive deficits and even trigger neurodegenerative diseases, with a prediction of chronic pain onset in an average of 7 years and fibromyalgia in 11 years (Irwin, 2019; Yi et al., 2022; Antonio Fagnani Filho, 2024 *In* II Alpha Meeting of Homeopathy).

In the Treatise on Chronic Diseases, about two hundred years ago, reactionary forms related to environmental conditions were already mentioned: social, family, emotional, climatic, hygienic, and dietary, maintaining the recurrence of illnesses. In this sense, with a view beyond the prescriptive and medicalizing vision, extensive work was developed in primary health care (Varricchio, 2023; Malfacini et al., 2024).

Recently, the clinical picture revealed during the Covid19 pandemic period was methodologically investigated by a researcher from the University of São Paulo, using the homeopathic similarity method, with several medications being identified according to the

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severity of the symptoms, and then a medication that covered the clinical syndrome of the epidemic genius was chosen, focusing on prevention (Teixeira, 2024).

CONCLUSION

The process of ultradilution and succussion through the classic Hahnemannian method of multiple vials was able to evoke secondary responses different from the primary responses described in the literature for the total ethanolic extract. It also obtained different results of *in vitro* and *in vivo* biological activities in the HUD 30CH potency when compared to the literature of HUD 30CH obtained from the grinding of latex.

The prelimnary results suggested a different mechanism of action for HUD 30CH from TM of *E. tirucalli* from Seropedica, whose evidenced that it was able to prevent intense oxidative stress in the group of challenged mice in relation to the control groups and also it was driven to lipidic metabolism (lipid peroxidation with endothelial lesion), which participate as mechanism in neurological, neoplasic and immunessupressive affections.

This could be a promising analysis for investigating new biological effects, such as sleep regulation and Systemic Arterial Hypertension. This is very important in a world with one billion people with chronic sleep disorders and their organic repercussions, in addition to the prevalence of approximately 75% of essential hypertension, whose etiology is undefined, both compatible with the pathophysiological descriptions that establish the Cancerinic State Syndrome. Basic research will go on.

LIMITS

Preliminary laboratory analysis (without repetition), whose evaluation led to the option of investigating different potencies of this pharmacotechnical preparation solely aiming at deepening the study of the mechanism of action in SAH of the Canceric State.

CONTRIBUTIONS

Previous preparations from latex grinding were active *in vitro* at HUD 30CH potency, being able to modulate enzymatic responses through the glycolytic pathway. Preliminarily, TM's HUD 30CH was not cytotoxic to cancer cell lines, did not induce cell hyperproliferation, nor did it reduce TNFα in cell lines and in serum of healthy female Swiss mice challenged in a chronic toxicology assay, suggesting a potential reducing effect on the inflammatory process and endothelial injury.

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Therefore, for the mitigation/drainage of the Cancerous State in patients using other official homeopathic medicines from the Brazilian Homeopathic Pharmacopoeia also authorized by ANVISA as ethical complementary medication, it is suggested that serum TNFα and CRP be used as biomarkers to monitor this biological and pharmacological action.

Regarding the development of healthy mice that used HUD 30CH of the total ethanolic extract (MT) *ad libitum* over eighteen weeks, parameters of specific directed lipid toxicity were preliminarily demonstrated, with possible installation of metabolic syndrome and Diabetes Mellitus.

The behavioral aspect was assessed qualitatively regarding mood – easy handling with absence of fear associated with increased exploratory activity suggesting stimulation of the cerebral cortex. It is noteworthy that deep sleep was observed in the test group, adopting the lined-up position, which leads us to question the possibility of an insertable effect in the classification of pathogenetic effect of this HUD. The dosages of tumor necrosis factor alpha, thyroid hormones, serotonin, glycosylated hemoglobin, cortisol, lipid profile and C-reactive protein should be performed in basic and toxicological research.

To better understand the mechanism of action, indicative of being “adaptogenic-like”, it is suggested to investigate chronic toxicology of HUD 30CH obtained from total aqueous extract of *E. tirucalli* from Seropedica and its controls, also from *Euphorbium officinarum* and *Euphorbia resinifera*, as used in Traditional and Indigenous Peoples' Medicine that dilute them in water, investigating in specific models to evaluate redox potential, lipid peroxidation and endothelial injury for verification and monitoring in case of installation of SAH.

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