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RESEARCH ARTICLE

HEMOXIGENASE-1, IRON, AND BILIRUBIN LEVELS AS OXIDATIVE STRESS INDICATORS OF COLLOIDAL SILVER EXPOSURE IN HUMAN LYMPHOCYTES

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Abstract

Introduction: Colloidal silver and nanoparticles (AgNPs) are used to disinfect fruits and vegetables as well as to purify water. Its consumption induces oxidative stress and activate antioxidant mechanisms such as catalase and heme oxygenase-1 (HO-1) at cellular level. The HO-1 attenuatesthe toxic effectsof metals andROSinvolved inchronic degenerative diseases.
Objective: Analyze the effects of Fe++ and bilirubin, products of HO-1 induction by exposure to Colloidal Silver (CS) and its association with oxidative stress parameters
Methods: A primary human lymphocytes were exposed to different doses 0.036µg /mL, 0.36µg/ mL and 3.6 µg/mL of colloidal silver and after of 0.5, 2 and 24 hrs, and HO-1 and its productsironand bilirubin were measurement, also protein levelsby colorimetric methods. Data wereanalyzed usingSPSS software, version18,to determinethe association betweenthe parameters
Results: TheCS increases HO-1 activity and was associated with bilirubin and iron R=0.518, p=0.0001. Moreover, ironwas associated with proteins levels, r=0.585 p0.0032, hydroxides r=0.390 p0.002, 8 – Iso r= 0.254 p.054, HO-1 r=0.518 p.0001, bilirubin r=.569 p.002 and tend to associate with cell viability r=-0.227 p.082. Also, Fe at theconcentration of 0.036µg/mL and low time exposurepresents association almost with all markers.
Conclusion: Colloidal silver at low concentration and times exposure induce HO-1 highly associated with bilirubin and Fe++, which plays an important role when triggering oxidation damage in the membranes,related with citotoxity. These results can be useful tools to study through Fe the OS development in the chronic degenerative diseases, by exposure to xenobiotics such as CS.

Introduction:-

The main effect of AgNPs is due to their metal quality, which alters electron transport and the functionality of proteins, indirectly causing genetic damage, altering and destabilizing cell homeostasis affecting mainly membrane proteins involved in cell regulation, primarily by producing oxidative stress(OS) by oxygen reactive species (ROS) and free radicals such as sulphite type derivatives, the participation of biochemical processes in metabolism

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degradation, increased synthesis of certain proteins such as HO-1, superoxide dismutase and catalase(1-3), in order to repair cell function.

Colloidal Silver (CS) in lymphocyte culture induces oxidative biomarkers, such lipid peroxides (LOOH), 8-isoprostanes and hydroxides (HO-), HO-1 and catalase, which impact both cell viability and proliferation, with a slightly higher protein concentration (3, 4). It is known that oxidative stress enables repairing mechanisms, one of which is the antioxidant enzymes production, such as HO-1, catalase and superoxide dismutase, which may be associated to protein synthesis.

In addition, metals, due to their affinity and protein binding, can act as haptens, trigger immunological response, and be immunotoxin, which is associated with the generation of free radicals, reactive oxygen species (ROS) and oxidative stress, all of which are involved in the lethal effects of necrosis and apoptosis connected to inflammatory processes (5, 6). They also bind proteins including metallothionines, ferritin and others. Metals operate as transcriptional factors, regulating genes required for the synthesis or degradation of biomolecules implicated in metal damage(7).

On the other hand, there is a strong association between HO-1 activity and 8 Isoprostane both increases (3). All isoprene's, terpenes and prostanoids, as well as arachidonic acid, are molecules that can be oxidized by the presence of double ligatures and attacked by free radicals and metals, causing rearranged molecules and an oxidative stress cascade are produced, altering the viability and cell signaling(8).

The HO-1 is an enzyme that converts the heme group, which is an essential component of hemoproteins (cytochromes and hemoglobin) to carbon monoxide (CO), and releases ferrous ion (Fe2) and produces biliverdin (BV), which is then converted to bilirubin (BR) by biliverdin reductase. These, HO-1 catabolized heme group products mediate the antioxidant, antiapoptotic, anti-proliferative, vasodilator and anti-inflammatory properties in humans (6), and may also mediate araquidonic oxidation(8).

Excess iron is thought to cause oxidative stress, which is defined an increase in the steady- state concentration of oxygen radical intermediates. Fe+ is also accumulated and liberated from globulins such as hemoglobin, myoglobin neuroglobulin, and probably HO-1, which not only regulates oxygen concentration, but also modulates oxidative stress through iron and Fenton reaction(9). For that, the main elements of iron metabolism, and the role of iron in lipid membrane damage by oxidation, and their involvement in the generation of inflammatory mediators(10). HO-1 is induced by a range of stressors, including medicines, metals, such as silver, ultraviolet radiation, hypoxia, hyperoxia, ischemia, and H_2O_2, as well as oxidative stress and glutathione depletion. Low expression has been detected in neuronal populations of the cerebellum, thalamus, hypothalamus, hippocampus, cerebral cortex and in the cerebral endothelium. However, it is the brain that colloidal silver, AgNPs and oxidative stress cause the most activation and erythrocyte lysis and heme release occur, while HO-1 expression in the brain is low (3, 6).

Therefore, the purpose of this research is to analyze the effect of colloidal silver in the induction of HO-1 activity and its products such as iron and bilirubin levels, all oxidative biomarkers, and their association with protein levels, cell viability and oxidative markers, previously reported by Avila Lagunes et al., 2021.

Methods:-

Biological Sample

A quantitative, experimental, multistage and analytical study was carried out in primary human lymphocyte culture from blood collection (10 mL) donated by one or several apparently healthy group O donors of both sexes, extracted with heparin anticoagulant. Lymphocytes were separated by centrifugation at 1500 rpm for 10 min and the donor serum were used to make the culture. Commercial colloidal silver at 0.36% was used.

Protein quantification

The Bradford method, standardized in microplates, was used. It was read at an absorbance of 595 nm. in a Spectra Max 190 Microplate Reader, where a standard curve of albumin at a concentration of 8 µg/µL was used. Data are expressed in µg/mL or mg/mL of proteins.

Enzymatic activity of HO-1

The mouse monoclonal antibody specific for HO-1 is pre-coated in plate wells, where HO-1 is captured by the immobilized antibody and is detected using a polyclonal HO-1 rabbit antibody. Subsequently, the polyclonal antibody is bound by a conjugated horseradish peroxidase secondary anti -rabbit IgG antibody. The assay was carried out using the tetramethylbenzidine substrate, which provides a precise blue color to the amount of HO-1 captured and was expressed in ng of HO-1 / mg of proteins. HO-1 activity was measurement by the indirect bilirubin quantification assay in the supernatant of the samples and bilirubin was detected at 450 nm. Data are expressed in mg of BB / mg of protein.

Iron Quantification

Quantification was carried out using the phenanthtronile technique, which measures free iron in the cell (Fe^{+2}), a control curve with iron sulfate 400 µg/mL was used. Data are expressed in mM of iron/mg of proteins.

Bilirubin quantification

Indirect method of HO-1 activity was quantified by differences in the measurement of wavelengths in the supernatant of the samples. In addition, the indirect bilirubin has an absorption peak of 450 nm. Data are expressed in mg of BB/mg of protein

Statistical analysis

Each experiment was conducted three times and expressed as mean ± standard error. The unpaired two-tailed t-student statistical test was performed on the raw data before converting them into percentages. Values of *p≤ 0.1, **p≤ 0.05 and ***p≤ 0.001 were considered as significantly. Correlation tests between the variables by Pearson or Spearman correlations were performed, GraphPad Prism, version 4.0 and SPSS version 18 were used.

Results:-

Colloidal silver increases protein concentration in human primary lymphocytes cultures

In the figure 1 it is shown that colloidal silver decreases significantly protein concentration at 0.5 hrs p≤0.01 and 2 hrs. p≤0.008 compared to time 0, except the concentration of 0.36 µgr/mL, which showed a significant increase at 0.5 and 24 hrs. While colloidal silver only increased at 0.5 hrs p <0.01, and significantly decreased p≤ 0.03 at 24 hrs vs control lymphocytes, all concentrations of colloidal silver showed a marginal increase p≤0.08, mainly 0.036 µg / ml. These values are contradictory to those expected due to the low viability and proliferation.

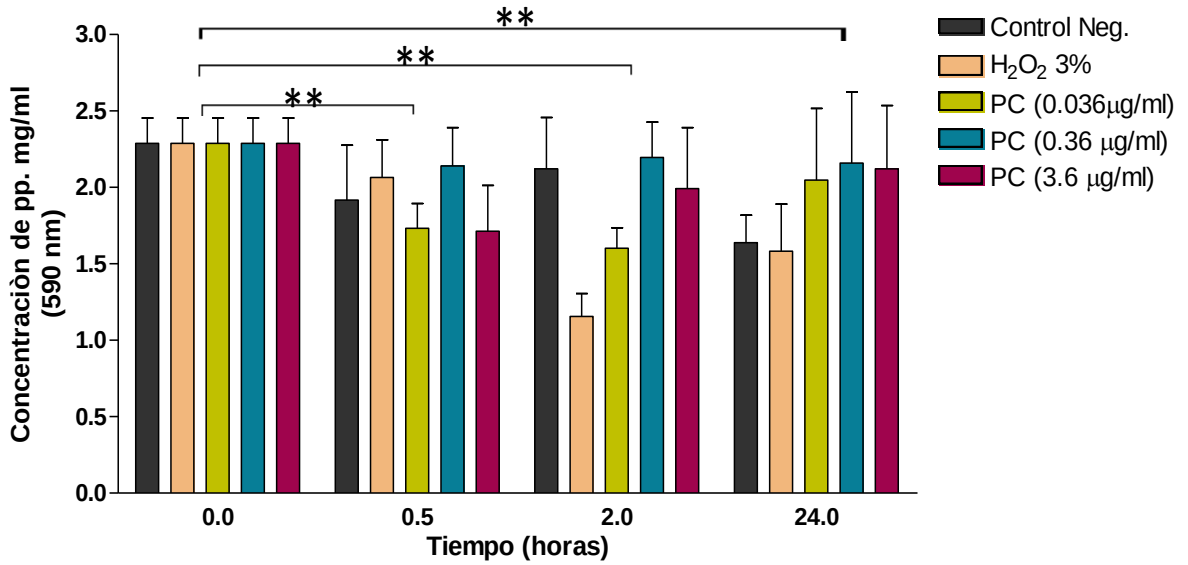

Figure 1:- Levels of proteins (pp) after colloidal silver treatments at 0.5 to 24 hrslymphocytes cultures. Data are expressed as mg/mL of proteins (pp). *p≤0.05; ** p≤0.05; *** p≤0.001 vs negative control, n=5 by duplicated.

Iron levels increases in lymphocytes exposed to colloidal silver

In the figure 2 iron concentration was measurement and at 0.5, 2 and 24 hr, iron level increased in all the treatments including its negative control in relation to time O. The concentration of 0.036 µg / mL colloidal silver increased iron levels at 2 and 24 hrs p <0.005, and marginal with the negative control. The concentration of 3.6 µg / mL, at 0.5 hrs and 2 hrs, increased and decreased, p≤ 0.050 significantly and marginally p≤ 0.08, iron concentration.The increased iron at 2 hrs with 036 µg / mL of colloidal silver, could be due to the slight increase in HO-1 at 0.5 hrs, while the increase in 3.6 µg/mL at 0.5 hrs could be due to the cell hemolysis by oxidative stress.

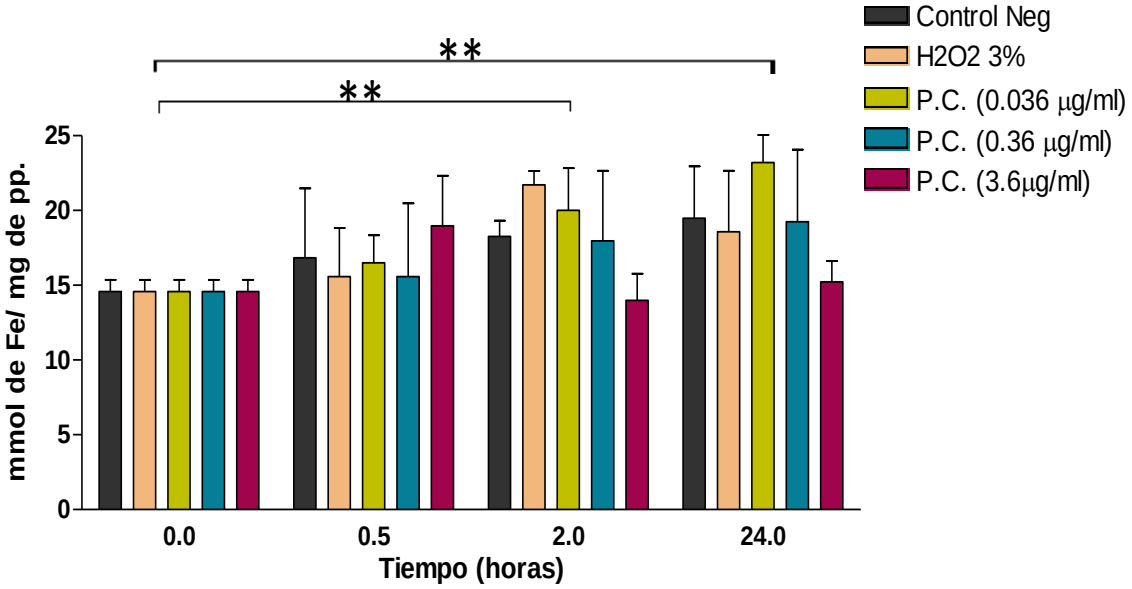

Figure 2:-Levels of iron after of colloidal silver treatment at 0.5 to 24 hrs in lymphocytes cultures. Iron quantification are represented as millimoles (mmol) of Iron/mg of protein (pp). *p≤0.05; ** p≤0.05; *** p≤0.001 vs negative control (vehicle), n=5 by duplicated.

Effect of colloidal silver in bilirubin level in primary lymphocytes culture

In the figure 3, due to the variability in the results and pronounced deviations, we found that at 0.5 and 2 hrs of colloidal exposition, bilirubin levels increases compared to negative control; in contrast with 3.6 µg/ml doses bilirubin levels decrease in all times, at difference to the 0.036 and 0.36 µg/ml doses of colloidal silver at 0.5 to 2 hrs due to tended to increase bilirubin levels p ≤0.09, similar to at 0.5 hrs compared with negative control and zero time.

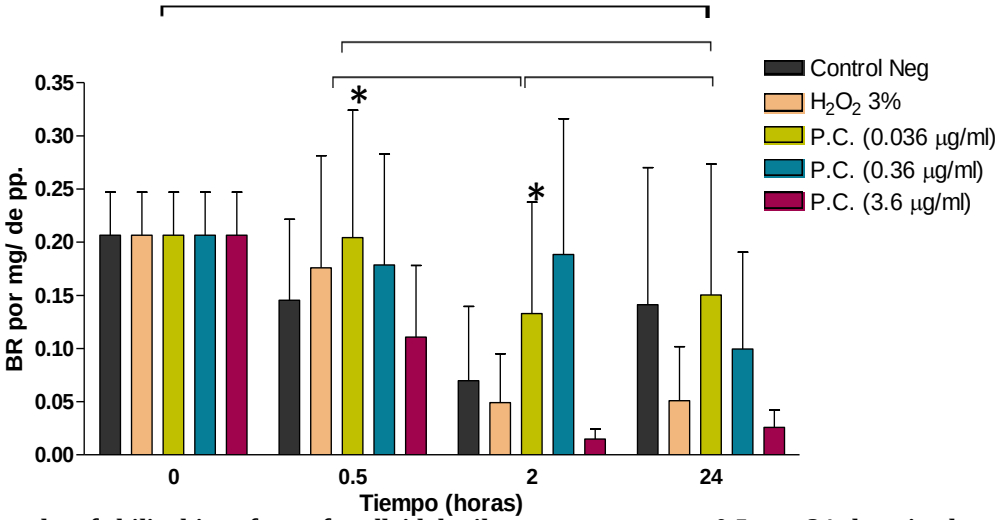

Figure 3:- Levels of bilirubin after of colloidal silver treatment at 0.5 to 24 hrs in lymphocytes cultures.Bilirubin quantification are represented as mg of bilirubin/mg of protein (pp). *p≤0.05; ** p≤0.05; *** p≤0.001 vs negative control (vehicle), n=5 by duplicated.

The little significant values and variations in bilirubin concentration could be because this is the product of biliverdin and depends on the activity of biliverdin reductase, also bilirubin has antioxidant effect. Furthermore, they both are very unstable and can act as antioxidants, counteracting the effects of oxidative stress, which induces colloidal silver and released Fe+.

Association between iron, bilirubin, protein concentration and parameters previously reported by (3), in primary lymphocytes cultures exposed to colloidal silver

In the table 1 its is show a positive correlation with protein concentration with the exposition time R = 0.515, p.0001. The increase proteins were associated with iron levels (r= 0.585 p<0.032) and exposition time (r= 0.515 p<0.001) and, as expected, they showed a negative association with viability (r= -0.391 p<0.001) and 8-Isoprostanes (r= -0.359 p<0.031) (this last results were previously reported in (3). Regarding induction of protein at 2 and 24 hrs, it does not correspond with the induction of 8-Isoprostanes, HO-1 and catalase due to colloidal silver effect, which only occurred at 0.5 h, with a decrease at 2 and 24 hrs.

The iron levels were positively correlated with 8-Isoprostanes (R=0.254, p0.05), hydroperoxides (R = 0.390, p=0.002) and HO-1 activity (R = 0.518, p.0001) and with exposition time (R = 0.319, p.013), except colloidal silver concentration. However, iron levels were positively correlated with protein increase. Although the induction of antioxidant enzymes, such as HO-1 and catalase, does not correspond to the increase in the concentration of proteins.

The bilirubin increase was associated positively with iron (R=0.569, p.002) and HO-1 (R=0.512, p .005) and negatively with exposition time (R= -0.308, p.005), viability (R = -.0 325, p=0.029), hydroxides (R = -0. 387, p=0.046), and marginally with proteins (R = -0.258, p=0.059 (Table 1). Iron might trigger oxidation damage in the membranes (lipid peroxidation hydroxides and 8-Isoprostanes), because the increased 8-Isoprostanes were highly associated with HO-1 (R =0.878, p<0.001) and iron (R=0.354, p<0.050).

Table 1:- Association between iron, bilirubin, protein concentration and parameters previously reported by Lucerito 2021.

		Protein	HO-1	Bilirubin	Iron	8-Iso	Hydro peroxide	MTT	Viability	Doses	Time
HO-1	**Correlation**		1	**0.518****	**0.518****	**0.878****		**0.267***		-0.210	-0.240
	p value			0.000	0.000	0.000		0.039		0.107	0.064
Iron	**Correlation**	0.585	**0.518****	**0.569****	1	**0.254***	0.390		-0.227		**0.319****
	p value	0.032	0.000	0.002		0.050	0.002		0.082		0.013
Protein	**Correlation**	1		0.258	0.585	**-0.359***	0.230		**-0.391****		**0.515****
	p value			0.059	0.032	0.031	0.07		0.001		0.001
Bilirubin	**Correlation**	0.258	**0.518****	1	**0.569****		**-0.387***	0.325*			**-0.308****
	p value	0.059	0.000		0.002		0.046	0.029			0.005

* P= 0.05; **p= 0.01

Discussion:-

The results previously reported showed that short times and low concretions of colloidal silver exposure are the most effective, in most markers of oxidative stress, specially HO-1, whose iron products and bilirubin play a very important role as an oxidative trigger in function of time and concentration correlated with the majority of oxidative markers(1, 3, 5, 6, 11, 12). Perhaps colloidal silver contacting the membrane label is the first mechanism to induce oxidative stress in cascade through the induction of HO-1 and iron release. Iron was correlated positively with increase in proteins, although the induction of antioxidant enzymes, HO-1 and catalase, does not correspond to protein increase. Fe+ increase and shown a positive association with HO-1, probably related to its activity, and with the increase of hydroxides and 8-Isoprostanes, which destabilize the membranes by oxidative stress production, where at 24 hrs, could regulate negatively the genetic expression of HO-1, by its own products as bilirubin or increase its degradation.

However, there is evidence since 1890 that iron has been playing a key role in cell division, where an increase in the nucleus and in cells that have a high proliferative activity at the time of division is observed (13-15). Perhaps its electronegative effects may be involved in Chromatin remodeling, or as protein bound such as transferrin, metalations. They could act as a transcriptional factor or with the response elements to induce genetic expression.Therefore, one of the major antioxidant defense strategies in aerobic organisms is to hijack iron in proteins to avoid the reaction of Fenton. It is known that iron regulate genetic expression, induce protein synthesis. Transferrin and ferritin and are involved in its transportation and storage in order to attenuate the reactive effects of iron. Without proper synchronization in these mobilization and neutralization mechanisms, oxidative damage would be more serious and the development of a large number of chronic degenerative diseases associated with oxidative stress would be at stake., and could be responsible of the seriously damage(9, 13).

The increase in proteins is most likely due to increased hydroxides, it is known that hydroxides induce protein synthesis and transcriptional factors such as NFK_{β}, which induces various mediators of the immune response such as interleukin, IL2, IL1 and the Kappa light chain of IgG,(16) which are involved in immune defense mechanisms, such as the induction of COX2. Increased 8-Isoprostanes is due to the non-enzymatic and non-specific oxidation of arachidonic because of silver andinflammatory lipid metabolites, prostaglandins, such as 8-Isoprostanes, have receptors that activate signaling pathways driving the development and progression of tumors(17, 18).

On the other hand, the increase in hydroxides could also because of the effect of colloidal silver on the induction of quinolic groups of the leukocyte NADPH oxidase, which is involved in electron transfer from NADPH to oxygen, and in the generation of reactive oxygenated species (ROS) such as O^{-2} and H_2O_2. Thus, NADPH and NADP oxidase will also be responsible for increased hydroperoxides and proteins in lymphocytes, since NADPH, a quinolic derivative, could also be a target of silver because of its similarity to its target, the ubiquinone(5, 6).Still there are several open key questions regarding the role of iron in oxidative stress in both, plants and animals. For example, it remains unknown the sources for Fe-catalyzed ROS, specificity (tissue and subcellular level) of iron-dependent oxidative stress, and the Fe-dependent oxidative stress signaling networks and antioxidant defense systems, as well as the previously exposure to contaminating xenobiotics that actives the chemistry defense and how are related.

Besides, immune and chemistry defense might be related and regulated by the same transcriptional factor, because in culture lymphocytes treated with colloidal silver the light chain induction kappa has been detected, as well as CYP450 2D6(5, 6). In addition, they both have a high homology, which has allowed us to propose that colloidal silver acts as an antigen and xenobiotic, presenting an association between the immune and chemical defense mechanism(19, 20).

When colloidal silver induces oxidative stress markers by iron release, then it represents a serious public health concern, since HO-1 induction and the presence of free radicals and ROS and 8-ISoprostanes are the common denominator in chronic degenerative non-infectious diseases, such as diabetes, heart disease, cancer and neurodegenerative diseases, Parkinson's, Alzheimer's, asthma and kidney diseases(21, 22). We must reflect on the consumption and abuse of colloids and metals given their interaction and activity with the cells of our organism and provide data about the reliability of their use, establish control and safety standards in silver derived products, which are marketed for bactericidal and therapeutic purposes indiscriminately(23).

Iron is associated to cell death called ferroptosis that is an iron-dependent oxidative stress has been discovered in mammalian cancer cells, also ferroptosis is related with lipid peroxidation generated through the Fenton reaction (24, 25). However several genes required to synthetize or degrade the compounds involved in ferroptosis, such as polyunsaturated fatty acid metabolism, amino acids, phospholipids, iron, glutathione (GSH), NADPH, and coenzyme Q10 (CoQ10), have been established recently in mammalian cells, for example GSH peroxidase 4 (GPX4) prevents ferroptosis by converting LOOH to non-toxic lipid alcohols (L-OH) and, thereby, reducing the accumulation of the toxic LO• that is generated from the LOOH reaction with Fe and CoQ10 oxidoreductase was identified as GSH-independent ferroptosis suppressor protein 1 (FSP1)(26). Also, this iron-dependent ferroptosis-like cell death pathway was also observed in plants during heat stress and pathogen responses (27).

The induction of oxidative stress by colloidal silver could represent a risk in the pathogenicity of microbes in the severe damage caused by the immune systems, such as in the pandemic by the SARS-CoV-2 virus, related to cytokine torment are associated to oxidative stress, such as IL1, IL6 as other, asking if that severity damage may

related with the previously exposure of NPs, which could have maintained mastocytes activation. colloidal silver has similar size to SARS-CoV-2 and other virus and it may be related with the ways to entrance to cells and the same signal related to oxidative stress(28-30).Regarding oxidative stress, more recent studies have shown that the normal accumulation and distribution of ROS acts as a redox-dependent signal to modulate many important biological processes such as cell division, cell expansion, cell differentiation, and immunity responses such as inflammation. Inflammation is an important contributor to the development and progression of human cancer. However, chronic inflammation causes the upregulation of a number of inflammatory cytokines, including IL-1β, IFNγ, and TNFα. The NFκB pathway is upregulated in many chronic inflammatory states, and evidence directly links the NFκB pathway to increased tumor formation and inflammation in experimental mouse models of intestinal cancer.

The results showed there was an increase of iron associated to oxidative stress markers and cell viability. And when analyzing and correlating the data of 8-Iso with previous results reported (3, 12), in an equal model, regarding the content of TBARS marker of lipoperoxides, a negative association was detected (R = - 0.528 p.026), as well as with hydroxides (R= -0.323 $p \leq <0.05$). This means when TBAR´s increase and hydroxides decrease 8-Isoprostanes, possibly the initial damage is induction of 8-Isoprostanes and HO-1, increasing iron, which in turn favors lipoperoxidation. Therefore, an increased production of hydroxides and a decrease of 8-Isoprostanes may facilitate an exit of 8-Isoprostanes to the medium, or they are involved in COX-2 induction. Thus, its decrease in the cell is observed. In any case, the initial damage of colloidal silver occurs in lipids of the membrane with production of 8-Isoprostanes and, consequently, of lipoperoxidation and hydroxides, which is in line with the significant induction at 0.5 hrs of stress markers (8-Iso , of catalase and HO-1), where 8-Isoprostanes show particularly a negative correlation as a function of time (R = -0.610, quite significant p <0.00000232), and the concentration of (R=-0.325 significant $p \leq 0.0242$), which suggests that the lower concentration, the higher concentration of 8-Isoprostanes.

Although colloidal silver is a potent bactericide, a good skin regenerator and a stimulator of the immune system, its excessive use could also cause in the not-too-distant future bacteria resistance, as in the case of antibiotics it also induces immunopathology. Thus, all of this causes other health problems related to infectious diseases, such as the increase in drug resistant strains as mycobacterium tuberculosis coupled with the fact that the constant induction of oxidative stress would increase immunotoxicity, neurotoxicity and hormonal disruption and be involved in the aggressive form of the immune response against virus and bacteria, such as SARS-CoV-2.

Conclusion:-

The lower concentration and exposure time of colloidal silver showed the greater effect on oxidative stress markers, where the concentration of iron related with HO-1 induction is one of the major responsible for oxidation because of its association with oxidative markers and protein synthesis. It is actively involved in the response of cultured lymphocytes to the effects of colloidal silver.

Competing interests

The authors declare that they have no competing interest.

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