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Protective effects of steroidal alkaloids isolated from *Solanum paniculatum* L. against mitomycin cytotoxic and genotoxic actions

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ABSTRACT

Solanum paniculatum L. is a plant species widespread throughout tropical America, especially in the Brazilian Cerrado region. It is used in Brazil for culinary purposes and in folk medicine to treat liver and gastric dysfunctions, as well as hangovers. Previous studies with *S. paniculatum* ethanolic leaf extract or ethanolic fruit extract demonstrated that they have no genotoxic activity neither in mice nor in bacterial strains, although their cytotoxicity and antigenotoxicity were demonstrated in higher doses. In order to assess the possible compounds responsible for the activities observed, we fractionated the ethanolic fruit extract of *S. paniculatum*, characterized by ^{1}H and ^{13}C NMR spectra, and evaluated two fractions containing steroidal alkaloids against mitomycin C (MMC) using the mouse bone marrow micronucleus test. Swiss mice were orally treated with different concentrations (25, 50, or 100 $mg.kg^{-1}$) of each fraction simultaneously with a single intraperitonial dose of MMC (4 $mg.kg^{-1}$). Antigenotoxicity was evaluated by using the frequency of micronucleated polychromatic erythrocytes (MNPCE), whereas anticytotoxicity was assessed by the polychromatic and normochromatic erythrocytes ratio (PCE/NCE). Our results demonstrated that steroidal alkaloids isolated from *S. paniculatum* strongly protected cells against MMC aneugenic and/or clastogenic activities as well as modulated MMC cytotoxic action.

Key words: anticytotoxicity, antigenotoxicity, Jurubeba, micronuclei, Solanaceae.

INTRODUCTION

The family Solanaceae comprises a large number of species with both toxic and pharmacological properties (Maruo et al. 2003, Mesia-Vela et al. 2002, Pereira et al. 2008). Many species of the genus *Solanum* are known by the local people in Brazil as "jurubeba", but the species *Solanum paniculatum* is described as the true "jurubeba" (Corrêa 1984). *S. paniculatum* L. (Solanaceae) is a neotropical weed of very common occurrence in Brazil, Paraguay, Bolivia, and Argentina, used in folk medicine and for culinary purposes (Missouri Botanical Garden 2010). The infusion prepared with "jurubeba" is a very common household remedy used throughout Brazil for hangovers because it exhibits anti-secretory gastric properties (Botion et al. 2005, Mesia-Vela et al. 2002, Sabir and Rocha 2008). Extracts of all parts of this plant

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are mentioned as anti-inflammatory (Mendes and Carlini 2007), antioxidant (Sabir and Rocha 2008), molluscicidal (Silva et al. 2005), diuretic, anti-herpetic, and hepatoprotective (Agra et al. 2007). Furthermore, a wine beverage is commercially available made from the fruits of *S. paniculatum* with an attributed medicinal purpose (Agra and Bhattacharyya 1999). The phytochemical analysis of *S. paniculatum* extracts showed that steroidal alkaloids are the major constituents, although resins and carbohydrates have also been isolated. The components and their contents vary according to the plant part (Ripperger et al. 1967, Schreiber and Ripperger 1966, Schreiber et al. 1965).

Recently, using the *in vivo* micronucleus test in mice and the SOS inductest in bacterial strains, our research team was able to demonstrate the cytotoxic activity as well as the absence of genotoxicity of *S. paniculatum* leaf and fruit crude extracts (Vieira et al. 2010a). Additionally, the antigenotoxicity was demonstrated only in the ethanolic leaf extract (Vieira et al. 2010b). Although previous studies with *S. paniculatum* extracts indicated that many compounds may well act synergistically, our data suggested that the antigenotoxicity exhibited by this plant could be related to an overall effect of the alkaloid compounds, since they are the major constituents of this species leaf extract and present antioxidant effect. The absence of antigenotoxic effect in *S. paniculatum* fruit extract may be due to the reduced content of alkaloids, because it decreases during the fruit maturation period (Siqueira-Jaccoud et al. 1982).

Since many bioactive metabolites from *Solanum* plants present pharmacological properties (Ikeda et al. 2000, Vieira et al. 2010c), the data supporting that *S. paniculatum* is a promising source of cancer chemoprevention agent (Endringer et al. 2010) and our interest in new active products prompted us to investigate the biological actions of *S. paniculatum* compounds. Thus, the present study aimed at evaluating the antigenotoxic and anticytotoxic effects of steroidal alkaloids isolated from *S. paniculatum* ethanolic fruit extract using the *in vivo* mouse bone marrow micronucleus test.

MATERIALS AND METHODS

Plant Material

S. paniculatum fruits were collected in Goiânia (16°37'40.94"S and 49°16'13.41"W), state of Goiás, Brazil, in September 2006, and identified by Dr. Heleno Dias Ferreira (Departamento de Biologia Geral, Instituto de Ciências Biológicas, Universidade Federal de Goiás). A voucher specimen was deposited at the Herbarium of the Universidade Federal de Goiás, under the number 30430/UFG.

Extraction and Fractionation

The fruits (257 g) were dried at 40°C in a stove with forced ventilation and exhaustively extracted with 70% aqueous ethanol (4 L) at room temperature. Ethanol was eliminated under reduced pressure at 35°C and the aqueous extract was partitioned with CHCl3. The aqueous layer was freeze-dried to obtain a dried extract (39.3 g), which was suspended in methanol yielding a soluble fraction (18 g). This was subjected to vacuum liquid chromatography (VLC) over silica gel using $CHCl_3$-MeOH-NH_4OH (3:1:1, 12:5:4, 6:3:2), to yield three fractions (SM1-3). SM3 fraction was chromatographed on Sephadex LH-20 eluting with MeOH-H_2O 50% to give 8 fractions (SM4-11). TLC: Merck aluminium sheets silica gel 60 F_{245}, $CHCl_3$-MeOH-H_2O (7:3:0.5), detection by Dragendorff"s reagent. ^1H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded in methanol-d_6 (TMS) on a Bruker Advance III-500 spectrometer. Jurubine 1H NMR (Fig. 1): δ 1.04 (H-1), 1.71 (H-1), 1.18 (H-2), 1.98 (H-2), 3.32 (H-3), 1.19 (H-4), 1.75 (H-4), 0.96 (H-5), 1.28 (H-6), 1.78 (H-6), 0.96 (H-7), 1.60 (H-7), 1.77 (H-8), 0.69 (H-9), 1.33 (H-11), 1.55 (H-11), 1.19 (H-12), 1.74 (H-12), 1.15 (H-14), 1.18 (H-15),

1.98 (H-15), 4.37 (H-16), 1.73 (H-17), 0.81 (H-18), 0.87 (H-19), 2.15 (H-20), 0.99 (H-21), 1.42 (H-23), 1.74 (H-23), 1.26 (H-24), 1.96 (H-24), 1.76 (H-25), 3.35 (H-26), 3.80 (H-26), 0.95 (H-27), GLUCOSE: 4.24 (H-1), 3.19 (H-2), 3.34 (H-3), 3.28 (H-4), 3.26 (H-5), 3.66 (H-6), 3.86 (H-6). ^{13}C NMR: δ37.0 (C-1), 31.2 (C-2), 47.8 (C-3), 39.0 (C-4), 44.8 (C-5), 27.3 (C-6), 32.2 (C-7), 33.4 (C-8), 53.6 (C-9), 36.2 (C-10), 20.7 (C-11), 39.8 (C-12), 41.9 (C-13), 56.1 (C-14), 31.3 (C-15), 80.9 (C-16), 65.0 (C-17), 16.7 (C-18), 12.3 (C-19), 41.1 (C-20), 15.9 (C-21), 113.8 (C-22), 31.6 (C-23), 28.6 (C-24), 34.7 (C-25), 75.9 (C-26), 17.3 (C-27), GLUCOSE: 103.2 (C-1), 75.3 (C-2), 78.1 (C-3), 71.5 (C-4), 77.2 (C-5), 62.9 (C-6).

Experimental Procedure

This study was approved by the Human and Animal Research Ethics Committee of the Universidade Federal de Goiás (CEPMHA/HC/UFG number 044/09). Healthy, young, male adult outbred mice (*Mus musculus* – Swiss Webster), obtained from the Central Animal House of the Universidade Federal de Goiás, were randomly allocated to treatment groups. All animals were brought to the laboratory 5 days before the experiments and housed in plastic cages (40 cm x 30 cm x 16 cm), in groups of five animals, in air-conditioned rooms at 22 ± 2°C and 50 ± 10% of relative humidity, with a 12-hour light-dark natural cycle. Food (appropriate commercial rodent diet Labina, Ecibra Ltda.) and water were given *ad libitum*. On the day of dosing, the animals were approximately 7-9 weeks old and weighing 25-35 g.

For each treatment, groups of five animals were orally treated with three different doses (25, 50, 100 mg.kg^{-1}) of *S. paniculatum* fractions (SM3 or SM7), and simultaneously co-treated with 4 mg.kg^{-1} intraperitonial (i.p.) mitomycin C (MMC, $C_{15}H_{18}N_4O_5$, Bristol-Myers Squibb, lot number 237AEL). The doses were estimated based on previous studies on determination of maximum tolerated dose (MTD). A positive (4 mg.kg^{-1} i.p. MMC) and a negative control (sterile distilled water) group were included. The animals were euthanized by cervical dislocation 24 h after the administration of the fractions and their bone marrow cells were flushed from both femurs in fetal calf serum (FCS, lot number 30721063, Laborclin, Campinas, Brazil). After centrifuging (300 x g, 5 min) the bone marrow cells were smeared on glass slides, coded for blind analysis, air-dried, and fixed with absolute methanol (CH_4O, lot number 55026, Synth, Diadema, Brazil) for 5 min at room temperature. The smears were stained with Giemsa (lot number 1081, Doles, Goiânia, Brazil), dibasic sodium phosphate ($Na_2HPO_412H_2O$, lot number. 982162, Vetec, Duque de Caxias, Brazil), and monobasic sodium phosphate ($NaH_2PO_4H_2O$, lot number 983831, Vetec, Duque de Caxias, Brazil) to disclose micronucleated polychromatic erythrocytes (MNPCE). For each animal, three slides were prepared and a minimum of 2,000 polychromatic erythrocytes (PCE) were counted to determine the frequency of MNPCE. Anticytotoxicity was evaluated by the polychromatic erythrocytes (PCE) and normochromatic erythrocytes (NCE) ratio (PCE/NCE). The slides were analyzed by microscopy (Olympus BH-2 10x100, Tokyo, Japan). The micronucleus test and MNPCE scoring were carried out according to Schmid (1973).

Statistical Analyses

In order to analyze the antigenotoxic activity of *S. paniculatum* fractions, the frequency of MNPCE in the treated groups was compared to the results of the positive control group by one-way ANOVA, and a value of $P < 0.05$ was taken as the criterion of statistical significance.

To evaluate the anticytotoxicity of the fractions, the PCE/NCE ratio of all treated groups was compared to the result of the positive control. A non-parametric Qui-square test (χ^2) was applied to determine the statistical significance of the results, and a value of $P < 0.05$ was considered significant.

RESULTS

Frequencies of MNPCE and PCE/NCE ratios obtained for mice bone marrow cells treated with *S. paniculatum* fractions and co-treated or not with MMC are summarized in Table I.

In this study, the negative control group (sterile distilled water) presented a low value of MNPCE, as already expected, and the positive control (MMC) caused a significant increase in MNPCE compared with the negative control ($P < 0.05$), confirming the sensitivity of the test.

The results of the antigenotoxic evaluation of *S. paniculatum* fractions showed a significant decrease in MNPCE for both SM3 (3.2, 3.8, and 3.6) and SM7 fractions (2.6, 2.8, 2.4) for all tested doses (25, 50, and 100 $mg.kg^{-1}$ co-treated with MMC) compared with the positive control ($\bar{x}$= 21.4; $P < 0.05$). Therefore, our results showed that these fractions of *S. paniculatum* fruit extract significantly modulate the genotoxic activity of MMC, demonstrating its antigenotoxic effect.

TABLE I
Frequencies of MNPCE and PCE/NCE ratio in bone marrow cells of mice treated with *Solanum paniculatum* SM3 or SM7 fractions and co-treated with mitomycin C (MMC).

Sample time and treatments		MN/2000 PCE (individual data)	MN/2000 PCE ($\bar{x} \pm SD$)	PCE/NCE ($\bar{x} \pm SD$)
MMC ($mg.kg^{-1}$)	Extract ($mg.kg^{-1}$)			
0	0	3, 3, 4, 3,3	$3.2 \pm 0.4^{(P<0.05)}$	$1.25 \pm 0.02^{(P<0.05)}$
4	0	32, 23, 20, 16, 16	21.4 ± 6.61	0.55 ± 0.10
SM3				
4	25	4, 3, 3, 3, 3	$3.2 \pm 0.44^{(P<0.05)}$	$1.04 \pm 0.17^{(P<0.05)}$
4	50	4, 4, 4, 3, 4	$3.8 \pm 0.44^{(P<0.05)}$	$1.01 \pm 0.22^{(P<0.05)}$
4	100	4, 5, 3, 3, 3	$3.6 \pm 0.89^{(P<0.05)}$	$1.28 \pm 0.10^{(P<0.05)}$
SM7				
4	25	2, 3, 3, 2, 3	$2.6 \pm 0.48^{(P<0.05)}$	$1.23 \pm 0.05^{(P<0.05)}$
4	50	3, 2,4, 3, 2	$2.8 \pm 0.74^{(P<0.05)}$	$1.27 \pm 0.04^{(P<0.05)}$
4	100	2, 3, 2, 2, 3	$2.4 \pm 0.48^{(P<0.05)}$	$1.29 \pm 0.04^{(P<0.05)}$

All the results were compared to the positive control group.
Significant difference compared with the positive control group ($P < 0.05$).
Non-significant difference compared with the positive control group ($P > 0.05$).

In relation to the anticytotoxic activity of *S. paniculatum* fractions, an increase in the PCE/NCE ratio was detected in both SM3 (1.04, 1.01, and 1.28) and SM7 fractions (1.23, 1.27, and 1.29) compared with the positive control group ($\bar{x} = 0.55$, $P < 0.05$). These results indicate that the co-treatment of the fractions, at all tested doses, in a period of 24 h, prevented the cytotoxic action of MMC.

DISCUSSION

Chemoprevention is a strategy for pharmacological intervention with naturally occurring and/or synthetic compounds that may prevent, inhibit or reverse carcinogenesis (Gupta 2007). Cancer chemopreventive agents may achieve these aims by modulating xenobiotic biotransformation or protecting cells from oxidative damage (Hail et al. 2008). *S. paniculatum* is a promising cancer chemoprevention agent (Endringer et al. 2010). The phytochemical analysis showed that this plant is a rich source of steroidal alkaloids such as jurubine, jurubidine, solamargine, solasonine, and solanine

(Ripperger et al. 1967, Schreiber and Ripperger 1966, Schreiber et al. 1965). Alkaloids are an important class of secondary metabolites, which have been reported to exhibit a wide range of pharmacological properties, including antimicrobial (Chakraborty and Brantner 1999, Fewell and Roddick 1993), antitumor (Ikeda et al. 2003), and anti-herpes effects (Ikeda et al. 2000). Plants synthesize these compounds to protect themselves against photosynthetic stress, reactive oxygen species (ROS), wounds, and herbivores. Based on food intake, these compounds form an important part of the human diet. Several reports in the literature describe alkaloids as being genotoxic (Ansah et al. 2005, Wang and Peng 1996). Nevertheless, there are also some studies that describe alkaloids as non-mutagenic (Proudlock et al. 2004) and even as anti-mutagenic (Villaseñor et al. 1997).

In order to evaluate the antigenotoxic and anticytotoxic effects of *S. paniculatum*, it was used mitomycin C (MMC). MMC is an antitumor drug that has been adopted due to at least two different processes responsible for its biological effects: DNA alkylation (which can lead to cross-links) and generation of free radicals, such as superoxide and hydroxyl radicals (which can lead to DNA strand breaks). The influence of such free radicals on the cytotoxicity of MMC is contingent on the extent of DNA damage induced by the given drug as well as on the ability of the cell to repair this DNA damage; however, cells have great difficulty to repair damage caused by the cross-linking of drugs with DNA (Kang et al. 2006, Menke et al. 2001). The modulation of mutagenicity and cytotoxicity by plant constituents can crucially alter the final effects of these compounds (Vilar et al. 2008).

In our study, two fractions (SM3 and SM7) of *S. paniculatum* fruit extract were evaluated against MMC genotoxic and cytotoxic actions by micronucleus test in mice. SM3 fraction contains two major steroidal alkaloids, which were evaluated by ^{1}H and ^{13}C NMR spectra. It was possible to identify one compound as Jurubine (Fig. 1), confirming the structure by comparison with data of Jurubidine (Bird et al. 1979, Chakravarty et al. 1983, Radeglia et al. 1977) and furostanol saponins (De Combarieu et al. 2003). The identification of the entire structure of the other compound was not completely elucidated; nonetheless, it proved to be a steroidal alkaloid with two glucose units in its structure and no spiro ring. The SM7 fraction was also evaluated indicating that jurubine was the steroidal alkaloid isolated in this fractioning.

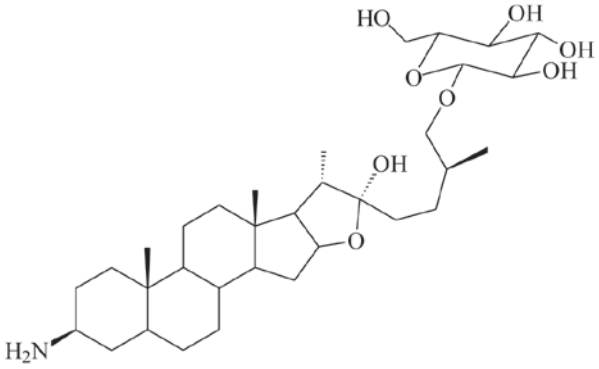

Fig. 1 - Representative structure of jurubine. Our group has isolated the compound from *Solanum paniculatum* fruits.

Our results demonstrated that *S. paniculatum* fractions acted effectively against the micronuclei (MN) induction when mice were exposed to MMC, suggesting that these steroidal alkaloids are antigenotoxic compounds. As the major steroidal alkaloid from SM7 is jurubine and both fractions presented antigenotoxic action, we may infer that at least the jurubine compound is responsible by antigentoxic action. The other steroidal alkaloid isolated from SM3 fraction possibly, also presents antigenotoxic effect. These results are in accordance with previous studies with alkaloids isolated from Solanaceae species that exhibited antioxidant action (Heo and Lim 2004, Whitaker and Stommel 2003).

The micronucleus test used in this study can also detect modulation of cytotoxic action by

the PCE/NCE ratio. Despite its wide spectrum of therapeutic use, MMC also possesses a wide spectrum of cytotoxicity to normal cells in humans and experimental animals (Vilar et al. 2008). When the normal proliferation of bone marrow cells is affected by a cytotoxic agent, such as MMC, there is a decrease in the number of immature erythrocytes (PCE) in relation to the number of mature erythrocytes (NCE) and the PCE/NCE ratio may decrease. Anticytotoxic agents cause an increase in this ratio or an attenuation of the cytotoxic effect (Rabello-Gay et al. 1991). As shown in Table I, both SM3 and SM7 fractions exhibited modulation of cytotoxic activity at all doses analyzed, demonstrating anticytotoxic effect. Since the cytotoxic action of chemotherapeutic drugs is ascribed mainly to their ability to induce genotoxic damage, in the present study, *S. paniculatum* alkaloids modulated MMC genotoxic action and, consequently, prevented cytotoxicity.

The family Solanaceae is rich in active secondary metabolites with antioxidant capabilities such as the steroidal alkaloids detected in our study (Whitaker and Stommel 2003). Antioxidant compounds can decrease oxidative stress, minimizing the incidence of genotoxicity (Antunes et al. 2005, Chu et al. 2002, Pellegrini et al. 2003). The mechanisms of the antioxidant action can include suppressing ROS formation either by inhibition of enzymes or by chelation of trace elements involved in free radical production (Halliwell and Gutteridge 1999). The antioxidant activity of *S. paniculatum* extracts, both in the crude or fractionated forms, was already demonstrated by Ribeiro et al. 2007.

In summary, the presence of steroidal alkaloids in *S. paniculatum* fractions caused attenuation of the genotoxic and cytotoxic actions induced by MMC. The steroidal alkaloid jurubine isolated from SM3 and SM7 fractions is the identified compound responsible by antigenotoxic and aticytotoxic actions.

CONCLUSION

The present study shows that low concentrations of steroidal alkaloids from *S. paniculatum* clearly exhibited the capacity to modulate genotoxicity and cytotoxicity induced by MMC in mice bone marrow. The steroidal alkaloid jurubine isolated from *S. paniculatum* is responsible by antigenotoxic and anticytotoxic actions. A final extrapolation of our work is that *S. paniculatum* steroidal alkaloids can attenuate the genotoxicity and cytotoxicity of substances with actions similar to those of MMC, which are found in our environment both as natural and anthropogenic products.

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RESUMO

Solanum paniculatum L., é uma planta com ocorrência em toda a América tropical, especialmente no Cerrado. No Brasil, é utilizada para fins culinários e, na medicina popular, para o tratamento de distúrbios gástricos e hepáticos, além de ressacas. Estudos com extratos de *S. paniculatum* demonstraram ausência de genotoxicidade em testes com camundongos e bactérias, apesar de promoverem citotoxicidade e antigenotoxicidade em altas dosagens. No intuito de detectar os compostos responsáveis pelas atividades observadas, o extrato etanólico dos frutos de *S. paniculatum* foi fracionado, os alcalóides esteroidais obtidos foram caracterizados por espectroscopia de ressonância magnética nuclear, e sua ação protetora contra mitomicina C (MMC) foi avaliada utilizando o teste do micronúcleo em medula óssea de camundongos. Camundongos foram tratados via gavage com diferentes concentrações (25, 50 ou 100 $mg.kg^{-1}$) de cada fração simultaneamente com uma dose intraperitonial de MMC (4 $mg.kg^{-1}$). A antigenotoxicidade foi avaliada pela frequência de

eritrócitos policromáticos micronucleados (EPCMN), enquanto a anticitotoxicidade, pela relação entre eritrócitos policromáticos e normocromáticos (EPC/ENC). Os resultados demonstraram que os alcalóides esteroidais isolados de *S. paniculatum* protegeram as células contra a ação aneugênica e/ou clastogênica de MMC, assim como, modularam sua ação citotóxica.

Palavras-chave: anticitotoxicidade, antigenotoxicidade, Jurubeba, micronúcleo, Solanaceae.

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