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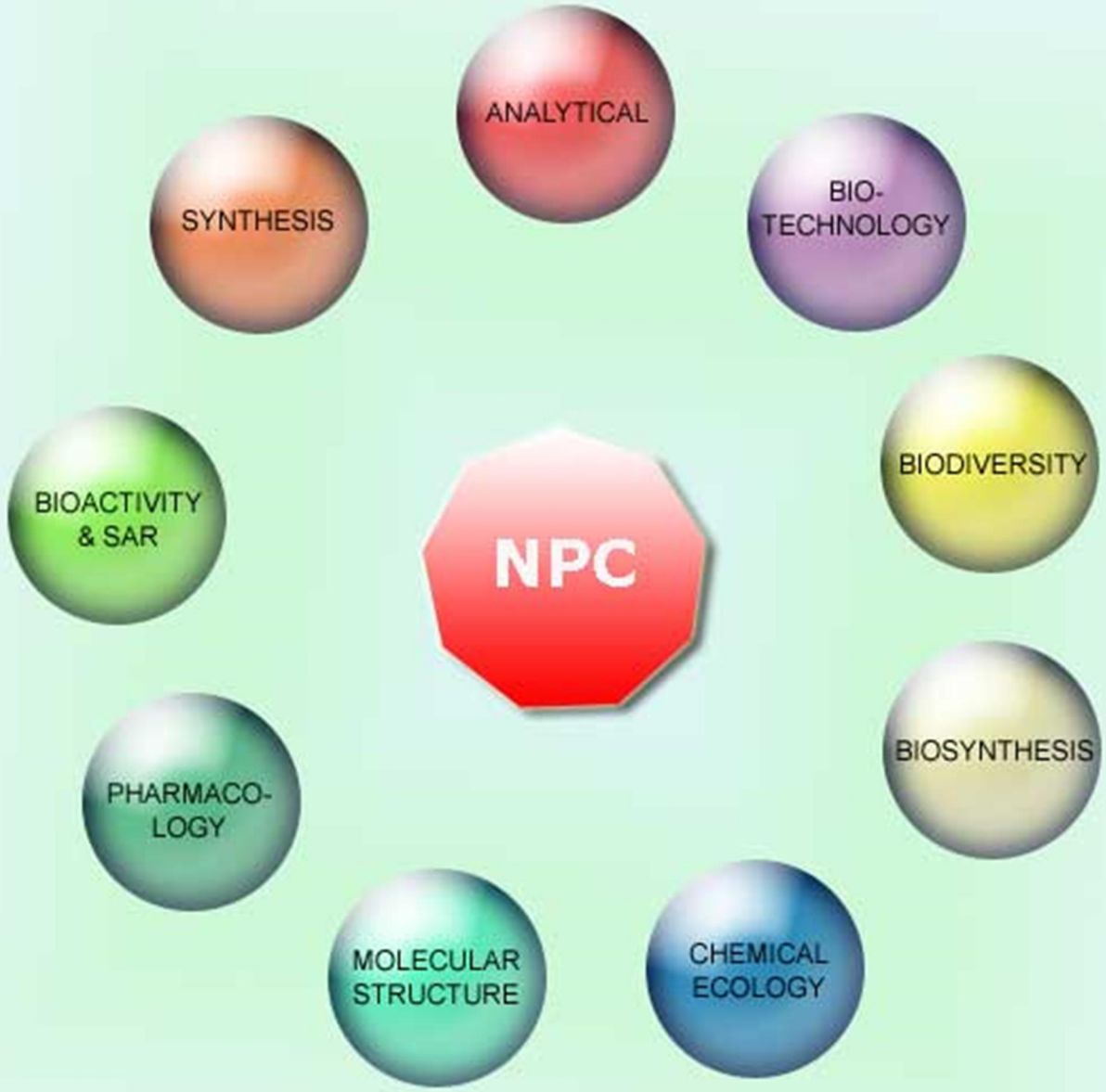

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Ruta graveolens Extracts and Metabolites against *Spodoptera frugiperda*

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The biological activity of *Ruta graveolens* leaf tissue extracts obtained with different solvents (ethyl acetate, ethanol, and water) and metabolites (psoralen, 2-undecanone and rutin) against *Spodoptera frugiperda* was evaluated. Metabolites levels in extracts were quantified by HPLC and GC. Ethyl acetate and ethanol extracts showed 94% and 78% mortality, respectively. Additionally, psoralen metabolite showed a high mortality as cypermethrin. Metabolite quantification in extracts shows the presence of 2-undecanone (87.9 µmoles mg^{-1} DW), psoralen (3.6 µmoles mg^{-1} DW) and rutin (0.001 µmoles mg^{-1} DW). We suggest that these concentrations of 2-undecanone and psoralen in *R. graveolens* leaf tissue extracts could be responsible for *S. frugiperda* mortality.

Keywords: Metabolites, Quantification, *Spodoptera frugiperda*, *Ruta graveolens*, Psoralen, 2-Undecanone, Rutin.

The fall armyworm, *Spodoptera frugiperda* (*Lepidoptera*: *Noctuidae* J. E. Smith), is a worldwide pest of economic importance for maize crops. This species can cause 20% of total crop loss from early developmental stages to flowering [1]. The most common method for controlling this pest is the use of synthetic insecticides such as chlorpyrifos, carbaryl, and cypermethrin [2]; however, this has led to environmental harm, increased cost of application, insect resistance, lethal effects on non-target organisms, and direct toxicity to consumers [3]. Therefore, the development of low-cost and environmentally friendly alternatives [4] is important.

Researcher groups have identified different natural compounds extracted from plants [5-7], and microorganisms that act as biological control agents in economically important crops such as maize, sorghum, and rice [7-10].

Ruta graveolens L. (*Rutaceae*) is a plant that produces metabolites with cytotoxic activity against microorganisms and insects [6, 7, 11, 12]. *This species contains alkaloids,* flavonoids, coumarins, furanocoumarins, tannins, volatile oils, glycosides, sterols and triterpenes [13-16]. Aqueous extracts of *R. graveolens* caused a mortality of 44% on *S. frugiperda* larvae [17], and essential oils tested at high concentrations produced 100% mortality; the identified compounds included nonanone (41.07%) and undecanone (45.89%) [18]. However, other extracts and metabolites of *R. graveolens* have not been evaluated for toxicity against *S. frugiperda* larvae. The aim of this work was to study the biological activity of *R. graveolens* extracts and metabolites (psoralen, 2-undecanone, and rutin) against *S. frugiperda* neonate larvae.

Initially, identification of *R. graveolens* was performed by amplification of the ITS region, corresponding to 700 bp [19]. The sample *R. graveolens* sequence was aligned with the corresponding sequence reported in GenBank (accession no. JQ230976.1); this sequence had a correspondence of 99% (Supplementary data).

Afterward, acuose, ethanolic and ethyl acetate extracts from *R. graveolens* were obtained and biologically evaluated on *S. frugiperda* larvae. We found that ethyl acetate and ethanol extracts caused a mortality of 94% and 78%, respectively, at a concentration of 1 mg/mL. Results show a significant difference among treatments ($P \leq 0.05$) (Figure 1). The aqueous extract did not show a significant difference with regard to negative controls (Figure 1); however, this extract caused a reduction in the weight of the larvae (0.055 to 0.050 g), indicating a reduction in the growth index of 8.36% in comparison with the control (data not shown).

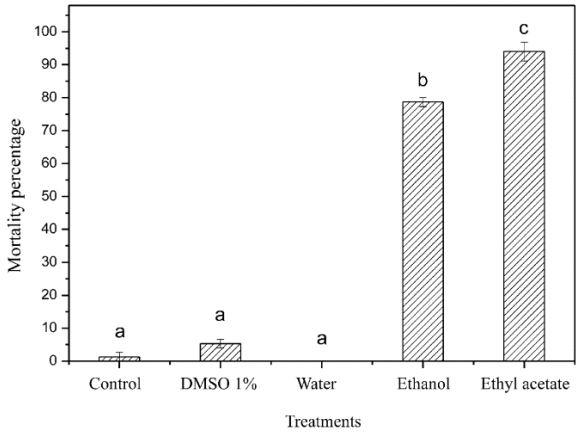

Figure 1: Percentage of *S. frugiperda* killed by *R. graveolens* leaf tissue extracts obtained with different solvents (water, ethanol and ethyl acetate). Extracts were integrated and homogenized at a concentration of 1 mg/mL of diet. Negative controls (diet only and diet + DMSO 1%). Larvae were collected after 7 days of treatment. The words represent the statistical analysis (Tukey test $P \leq 0.05$) between the means of each treatment.

According to previous reports, psoralen, 2-undecanone, and rutin have been found as the main metabolites of *R. graveolens* extracts [13, 15, 20, 21]. Therefore, these metabolites were evaluated on *S. frugiperda* larvae. The bioassays of psoralen, 2-undecanone and rutin metabolites showed that psoralen is highly toxic, killing 100% of *S. frugiperda* larvae as cypermethrin insecticide (Figure 2). The second most toxic metabolite was 2-undecanone, which caused 50% mortality. Rutin did not show a significant difference with regard to negative controls (diet only and diet + DMSO 1%) (Figure 2). Some authors have documented that rutin by itself does not have activity, but in combination with other flavonoids, its biological activity may increase [22].

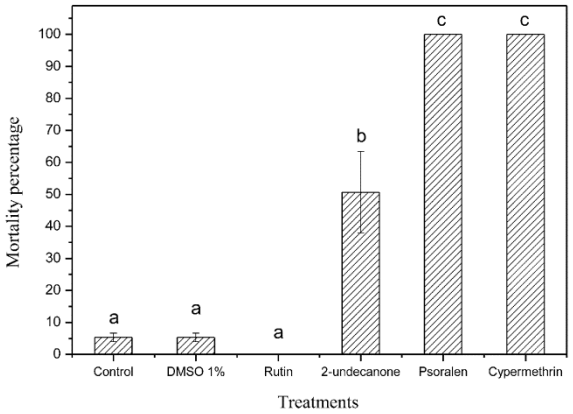

Figure 2: Percentage of *S. frugiperda* killed by standard metabolites. Metabolites (psoralen, 2-undecanone and rutin) were integrated and homogenized at a concentration of 1 mg/mL of diet. Negative controls (diet only and diet + DMSO 1%), and positive control (cypermethrin). Larvae were collected after 7 days of treatment. The words represent the statistical analysis (Tukey test $P \leq 0.05$) between the means of each treatment after 7 days of treatment.

Researchers have reported that psoralen at a low concentration (2 µmoles/mL) in celery inhibits the growth of pathogens such as *Botrytis cinerea*, *Alternaria alternata* and *Sclerotinia sclerotiorum* [23], while high concentrations (587.2 µmoles/mL) cause a mortality of up to 80% of *Leptinotarsa decemlineata* (Say) larvae [24]. Additionally, it inhibits microbial activity [25], and is involved in physiological [26] and molecular responses [27, 28]. In humans, psoralen has been widely used orally for psoriasis; however, it has resulted in adverse effects, including skin cancer after long-term use [27, 29, 30] discussing its potential use as a bioinsecticide [31-33]. However, KINGBO® a botanical insecticide containing psoralen, has been used in laboratory bioassays against larvae (*Tetranychus urticae* Koch) in a combination (0.2% oxymatrine + psoralen 0.4%) with a LC_{50}= 6.88 µL/L [33, 34]. Taking into account the work and criteria of different authors in the use of psoralen, we cannot discard the use of psoralen as a botanical insecticide.

In the case of 2-undecanone, it has a significant role in the glandular trichomes of *Lycopersicon hirsutum f. glabratum* [35]. It acts as a defense mechanism against herbivorous insects [36] and as a repellent against various arthropods [37-39]. The use of 2-undecanone as an insect repellent against various arthropods is relatively new [38, 39] and it has been shown that these properties occur at high concentrations [37]. Also, it was recently shown that 2-undecanone can act as an olfactory agonist or antagonist, modulating odorant receptor activity [40]. This information suggests that in approximately 50% of the larvae of *S. frugiperda*, 2-undecanone modulates odorant receptor activity, causing larvae not to feed, which resulted in a weight loss of 8.6%.

Finally, to establish a correlation between biological activity and the presence of metabolites in extracts of *R. graveolens,* the conditions for detection and quantification of 2-undecanone, psoralen and rutin by HPLC and GC were established. The retention times for the metabolites were 24.62, 11.17, and 5.99 min, respectively. In the extracts analyzed, 2-undecanone was the metabolite with the highest concentration, followed by psoralen and rutin (Table 1). A comparison of the amount of each metabolite present in the extracts suggested that each compound could be extracted with a specific solvent. The most efficient solvent was ethyl acetate, which quantified high levels of 2-undecanone and psoralen. In phytochemical analysis, it has been reported that the concentrations depend on the polarity of the solvent and the extraction parameters [41].

Table 1: Metabolite concentration in *R. graveolens* leaf tissue (µmoles mg^{-1} DW) [a], obtained with three different solvents.

Solvent	Psoralen	(SE±) [b]	Rutin	(SE±) [b]	2-undecanone	(SE ±) [b]
Ethyl acetate	3.6	0.2	0.001	0.000	87.9	6.1
Ethanol	3.0	0.04	0.02	0.003	86.2	9.7
Water	0.2	0.03	0.02	0.001	0.0	0.0

[a] Concentration of metabolites µmoles mg^{-1}/DW (Dry weight). [b] Standard error (SE ±).

Also, a correlation between the decrease in metabolite concentration and mortality was observed. Therefore, we suggest that the toxic potential of ethyl acetate, and ethanolic extracts could be caused by high concentrations of psoralen and 2-undecanone. Additionally, our information indicates that low concentrations of psoralen, compared with 2-undecanone, are sufficient to be lethal against *S. frugiperda*.

Conclusions: In this work, ethyl acetate extract from *R. graveolens* leaf tissue showed the highest percentage of mortality against *S. frugiperda*. Psoralen metabolite showed the same toxic effect as cypermethrin. Additionally, our results suggest that 2-undecanone could be used in the generation of new botanical insecticides against *S. frugiperda.* However, studies of its secondary effects and mechanism of action are necessary.

Experimental

Molecular identification of R. graveolens: Extraction of DNA from leaves (12 mg) was performed with the Wizard® Genomic DNA Purification Kit, (A1120, Promega Corp., Madison, WI). PCR was performed using the primers ITS1-Fwd (5'-TCCGTAGGTGAACCTGCGG-3') and ITS4-Rev (5'-TCCTCCGCTTATTATTGATATGC-3'). The PCR assay was performed with 12.5 µL of GoTaq Green Master Mix (2X) (M7122, Promega Corp.), 1 µl of each oligonucleotides (5 µM) and 1 µl of genomic DNA (25 ng) in a final volume of 25 µL. PCR conditions were as follows: 94°C for 5 min, followed by 35 cycles of 95°C for 30 s, 58°C for 30 s, and 72°C for 1 min, and final step of 72°C for 7 min. The product was direct sequenced on the 3130 Genetic Analyzer (Applied Biosystems, HITACHI Tokyo, Japan) with ABI PRISM® BigDye® Terminator v3.1 Cycle Sequencing Kits (P/N 4336917, Applied Biosystems, Foster City, CA). The sequences were assembled using SeqMan software of the LaserGene 8 package (DNASTAR, Madison, WI), and analyzed with Blast from GenBank (www.ncbi.nlm.gov) (see details in Supplementary data).

***Extraction*:** Fresh leaf tissue (100 g) was obtained from *R. graveolens*. Collected material was washed, dried at 25°C for 30 min, and ground (Osterizer, 450-10) for 5 min. For each treatment, 100 mL of extraction solvent was added 3 times (ultrapure water; Milli-Q® ZMQS6V001, ethanol; Reproquifin PQF® 10-333, ethyl acetate; Reproquifin PQF®, R-004) every 24 h for 3 days and kept in the dark at 25°C to recover the soluble phase. After the solvent was added, the mixture was stirred for 1 min. The mixture was then filtered using Whatman #1 paper and afterwards transferred to a round-bottom flask (250 mL) and placed in a rotary evaporator at 55°C and 180 rpm. The extract concentrate was stored at 4°C in darkness until use. One mg dry weight (DW) sample was resuspended in 1 mL of methanol and passed through a Millipore filter (0.22 µM) for subsequent analysis.

Metabolite quantification: High-Performance Liquid Chromatography (HPLC) was used to determine the concentration of psoralen and rutin. The calibration curve for each standard metabolite was performed using psoralen (Sigma Aldrich P8399), and rutin (Rutin hydrate, Sigma Aldrich R5143). The retention time of each compound was used to compare the retention time of the compounds present in each extract. The chromatographic system

(Agilent Technologies 1100) consisted of a quaternary system of pumps (Agilent Technologies G1310A) connected to an automated sample injector (Agilent Technologies G1313A). Psoralen and rutin were detected using a wavelength of 254 nm. The injected samples were detected with an ultraviolet detector (Agilent Technologies G1314A), and a reverse phase C_{18} column (Kromasil 5 µm, 4.6 mm inner diameter × 250 mm). For detection of psoralen, the mobile phase was MeOH/H_2O (25:75) and for rutin, MeOH/H_2O (95:5). The flow rate for all samples was 0.5 mL/min. The column temperature was kept constant at 25°C. Solvents used were previously degassed (ultrapure water; Milli-Q® ZMQS6V001, ethanol; Fermont H6122, ethyl acetate; Reproquifin, R-004).

An Agilent 7890A series Gas Chromatograph (GC) system equipped with a hydrogen flame ionization detector was applied for quantitative analysis of 2-undecanone (Sigma Aldrich W309311). Separation was achieved with an Agilent HP-INNOWAX column (30 m × 0.530 mm, 1.00 µm), Agilent Technologies. The carrier gas was nitrogen with a flow of 2 mL/min. The oven temperature was programmed at 60°C for 5 min, with a rise of 5°C/min up to 210°C and held for 5 min. The temperature of the injector and detector were set at 150°C and 250°C. The split less injection volume was 2 µL. A stock solution of 2-undecanone was prepared in ethyl acetate at a concentration of 1 mg/mL and stored at 4°C before use.

Bioassays: *S. frugiperda* neonate larvae were provided by the insect rearing area of the CBG-IPN. Bioassays were conducted with neonate larvae on an artificial diet. Nine treatments were tested: aqueous, ethanolic, and ethyl acetate extracts, negative controls (diet only and diet + DMSO 1%; Sigma Aldrich P-5879), positive controls (cypermethrin; IQC, S.A. de C.V.), and standard metabolites: psoralen, 2-undecanone, and rutin. Psoralen and rutin were dissolved in 100 µL of DMSO 1%, and 2-undecanone was dissolved directly in the diet. Extracts and standard metabolites were integrated and homogenized in diet at a concentration of 1 mg/mL, and 5 mL of the mixture was dispensed in plastic cups (p100-100, SOLO). Controls were prepared in the same way. One neonate larva was transferred with a camel hair brush to one cup. Twenty-five cups were placed in a paper bag and incubated for 10:14 h; light/dark at 27 ± 1°C and 65 ± 5% RH. Bioassay was performed in triplicate totaling 75 larvae per treatment; mortality was recorded 7 days after treatment. Growth inhibition was calculated accordingly [42].

Statistical analysis: Data were analyzed and plotted with SAS/STAT® (Statistical Analysis Software) and Origin 9.1 Software (Data Analysis and Graphing Software). An analysis of variance (ANOVA) was made and the degree of significance between the mean values was determined using the Tukey test with P values ≤ 0.05 being considered significant.

Supplementary data: Details on the amplification and aligned ITS sequences of *R. graveolens*.

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