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Review Article

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A Review on *Solanum torvum* Swartz.

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ABSTRACT

Solanum torvum Swartz (family: Solanaceae) is commonly known as turkey berry. This plant is found in tropical Africa, Asia and South America. *S. torvum*, is an important medicinal plant in tropical and subtropical countries. It is widely used like food and in folk medicine around the world. Traditional medicinal uses of *S. torvum* were recorded in the Ayurveda and Chinese pharmacopeia. The present review covered the plant morphology macroscopically, the chemical constituents and the pharmacological properties of *S. torvum*. This has included therapeutic effects of the whole plant and its extracts, fractions and isolated compounds. Antimicrobial, anti-ulcerogenic, antiviral, anti-platelet aggregation, antioxidant, analgesic, anti-inflammatory, systolic blood-pressure modification, cytotoxic and other activities have all been described through previous research studies carried out using different in-vitro and in-vivo bioassay techniques. This supported the claims of the therapeutic utility of the species.

Keywords: *Solanum torvum* Swartz, Solanaceae, food, folk medicine, therapeutic utility.

ARTICLE INFO

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1. Introduction

Podophyllotoxin [1] (Figure 1) and its several analogues are being used as cytotoxic spindle poisons and antitumor

agents at clinical levels [2]. Several analogues of the podophyllotoxin have been reported in literature.

Podophyllotoxin has been extracted from two important medicinal plants named *podophyllum emodi* an Indian species and *podophyllum peltatum*, a North American species [3]. It also occurs in many other plants of podophyllum species. It belongs to the family of natural products called lignans. Podophyllotoxin showed other biological activities such as cathartic, antitropical skin disease, antimalarial, anti-HIV (AIDS) etc. [4]. In view of the above facts, it was decided to modify the structure of podophyllotoxin and synthesized tetralone acids as analogues [5-8]. They were synthesized by replacing 3,4,5-trimethoxyphenyl ring with cyclohexyl group in podophyllotoxin and 1,3-methylene dioxy ring with methoxy, methyl, thiomethyl group and hydrogen and fluorine elements and lactone ring with carboxylic acid group. The analogues of podophyllotoxin were synthesized using Gensler's method [9] with some changes in reagents and experimental procedure. The synthesized tetralone acids were screened for their antimutagenic activity by onion root method [10].

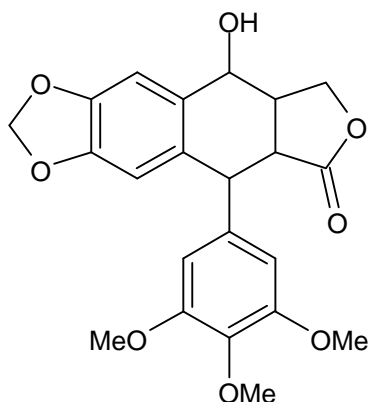


Figure 1: The structure of podophyllotoxin.

2. Materials and Methods

2.1. Materials and methods

All the reagents and chemicals were purchased. They were used without further purification. Melting points were taken in open capillary tubes and are uncorrected. Thin layer chromatography (TLC) is performed with E. Merck pre-coated silica gel plates (60F254). Acme, India silica gel, 60-120 mesh is used for column chromatography. IR spectra in KBr were recorded on Perkin-Elmer model 683 spectrometers. ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) spectra were recorded using tetramethyl silane (TMS) as an internal reference on Bruker spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400. Mass spectra were obtained by Water-Q-TOF ultima spectrometer. Micro analytical data were obtained by Elemental-Vario EL-III.

2.2. Synthesis

2.2.1. Procedure for the preparation of substituted Phenyl (3, 4, 5 trimethoxyphenyl) methanone (2a-e).

A Grignard reaction was prepared in an oven dried three necked flask outfitted with a reflux condenser, dropping funnel and magnetic stirrer. Approximately 1/4th of a 10mmol aliquot of 1-bromo-3, 4, 5-trimethoxybenzene in

5ml of anhydrous THF was added to a mixture of Magnesium turnings (10mmol) in 2.5ml of anhydrous THF with a small piece of iodine. As soon as the reaction mixture becomes colourless the remaining 1-bromo-3, 4, 5-trimethoxybenzene solution was added drop wise to the solution under mild reflux stirring was then continued for 1h at room temperature. A (trimethoxyphenyl) magnesium bromide solution (10mmol) was added slowly to the substituted benzaldehyde (a-e) 8.35mmol in 2.5ml anhy. THF solution at 00C. after complete addition, the solution was allowed to stir at room temperature for another 20min. a saturated ammonium chloride(10ml) solution was added to hydrolyze the adduct at 00C and the mixture was stirred for 10min. the phases was separated and the aqueous layer was extracted with ether (10ml in three portion) the combined organic layer were stirred washed with brine solution and dried over MgSO₄ and filtered the filtrate was concentrated in vacuum and the residue was purified by recrystallization.

2.3. Antimitotic study

The antimitotic activity of synthesized analogues of podophyllotoxin was examined by the onion root tip method. The ID₅₀ (concentration for 50% inhibition of mitosis) was determined as follows.

2.3.1. Materials and method:

Orcein solution: 1g orcein dissolved in 45% acetic acid at boiling temperature, maintained for 5min at the same temperature then cooled to room temperature and filtered. The filtrate was used for staining.

Hydrochloric acid 0.1N:

Test solution: prepared by dissolving the exactly known weight (0.001-0.003g) of the synthetic analogue in 3ml of absolute ethanol and diluted with distilled water to 250ml in a standard flask. All the synthesized products to be tested gave a clear solution in the above process.

2.3.2. Method: Onion base was immersed into an extent of half a centimeter in a sample tube (7*3cm) after removing the old roots from it and the immersion continued for two days for germination. After two days germinated root tip were removed and placed on the sample tube containing fixing solvent [absolute ethanol- glacial acetic acid, 3:1 (v/v)]. After 24hours fixing solvent was decanted carefully and the root tips were washed with preserving solvent (70% ethanol) and kept immersed in the same solvent. An onion also allowed to germinate in a controlled solution (3ml of absolute ethanol diluted with distilled water to 250ml) without the synthetic analogues in exactly the same as was done in preparing solution of synthetic analogues. Root tips were placed on a clean watch glass containing the stain solution (orcein-HCl solution is 7:1 v/v) and heated on the flame until fumes comes out. It was then placed on the micro slides. A drop of stain solution was added and the root tips were squashed by a razor blade and slides were prepared.

2.3.3. Antimitotic assay: The prepared slide was mounted for an observation under a compound microscope. The total number of cells and the number of dividing cells were counted. The percent of the number of dividing cells compared to the control and the percent inhibition of mitosis by the test antimitotic agent at the given

concentration against a control were calculated. The inhibition studies for each synthetic product were done for 3 different concentrations. The statically data are present in table1. Mitotic Index (MI) was calculated by following method of Fissceja [12]. The mitotic index was determined by examination of minimum of zone cells. Three replicates were made for each calculation. The slides were observed under microscope and photographed.

M.I. = (Total number of dividing cells / Total number of cells examined) x 100

The percentage of the number of dividing cells compared to the control and the percent inhibition of mitosis by antimetabolic agent at a different concentration such as 100, 200, and 400×10^{-6} mol/L against a control were calculated. The concentration needed for 50% inhibition (ID₅₀) was extrapolated from the graph of the concentration versus percentage inhibition. ID₅₀ values for novel tetralone acid analogues of podophyllotoxin for antimetabolic activity were calculated individually following hakala [13] method.

3. Results and Discussion

3.1. Chemistry

The tetralone acid analogues of podophyllotoxin were synthesized by gensler's method (Scheme 1). Substituted Phenyl (3, 4, 5 trimethoxyphenyl) methanone (2a-e) were prepared in high yields by grignard reaction. The esters (3a-e) were prepared by Stobbe condensation of substituted Phenyl (3, 4, 5 trimethoxy phenyl) methanone (2a-e) with diethyl succinate using potassium tert-butoxide in tert-butyl alcohol [15]. Substituted Phenyl (3, 4, 5 trimethoxyphenyl) methylene succinic acid (4a-e) were prepared by Hydrolysis of (3a-e) with HBr in refluxing acetic acid affords substituted 4-(3,4,5-trimethoxyphenyl)-4-phenylbut-3-enoic acid which is hydrogenated with H₂ over Pd/C in ethyl acetate giving 4-(3,4,5-trimethoxyphenyl)-4-

phenylbutanoic acid (VII), which is converted into the corresponding acyl chloride (VIII) with refluxing SOCl₂. Cyclization of (VIII) with AlCl₃ in CS₂ yields 4-(3,4,5-trimethoxyphenyl)-3,4-dihydro-1-(2H)-naphthalenone (IX). The products were characterized by IR, ¹H NMR, ¹³C NMR, mass spectral data and elemental analysis data. Tetralone acids 7a and 7c were obtained in good yields (65-68%). The products 7b, 7d and 7e were formed in moderate yields (50-53%). The formation of moderate yield might be due to the less electron donating nature of hydrogen, methyl and fluorine linked phenyl ring. Hence the π -electrons of benzene ring are not readily available for Friedel-Craft's intramolecular acylation reactions. The NMR spectrum of tetralone acid 7a showed a triplet at 3.3-3.6 ppm (J = 6 Hz) for the C1-H. The large coupling constant (J) value indicated that C1-H and C2-H in 7a were diaxial. Hence the C2-H carbonyl and C1-H cyclohexyl groups should be trans to each other, a configuration being thermodynamically more stable.

3.2. Antimetabolic activity

As regards the relationships between the structure of the podophyllotoxin scaffold and antimetabolic properties, it showed varied antimetabolic activity (Table 1). The presence of different substituent on the ring A causes a certain changes in activity. The compound 7b has hydrogen, moiety on ring A, which is accounted for the enhanced antimetabolic activity than when compared to control solution. Similarly compounds 7c and 7e have showed significant activity. The compounds 7c and 7e have methyl and fluorine moiety on ring A, which is accounted for the moderate activity of the compounds. On the other hand, the remaining compounds 7a and 7d have showed less activity compared to control. From the obtained results, it is clear that the major role for antimetabolic activity is played by substituents on ring A moiety. It is evident that novel tetralone acid analogues of podophyllotoxin were showed good antimetabolic activity.

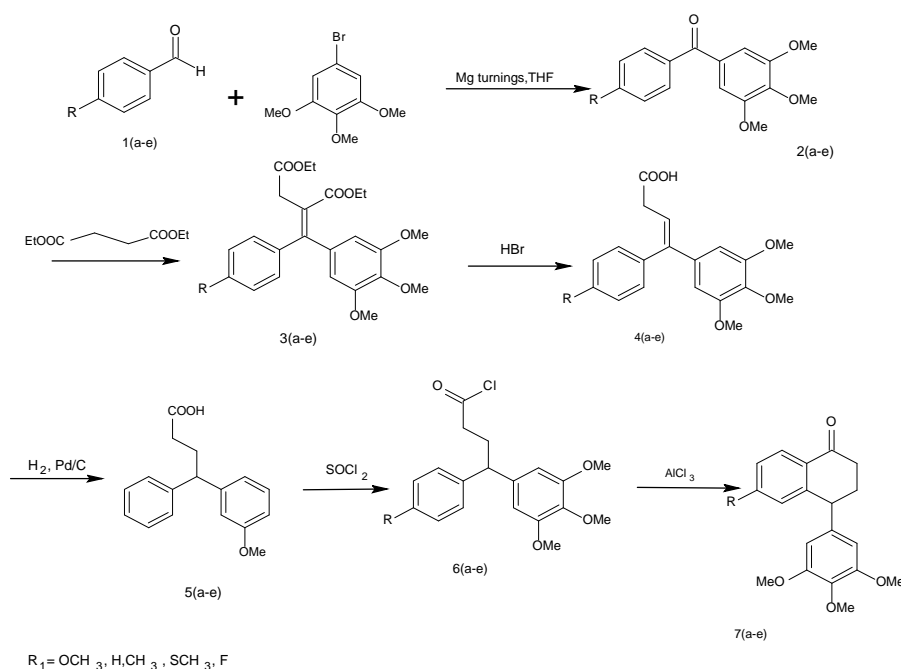


Table1: Antimitotic activity of the compounds (7a-e) by onion root tip method

Compound	Concentration in ml/mg	Total number of dividing cells	Total number of cells	% dividing cells	average	% of dividing cells compare to control	% of inhibition compare to control	ID50 mmol/L $\times 10^{-6}$
Control solution (1.2% alcohol)		55	210	26.19	21.493	100	0	0.0
		36	216	16.66				
		48	222	21.62				
1	1.44	18	202	8.911	16.71	77.75	22.25	3.24
		46	230	20.00				
		52	245	21.22				
7a	1.19 2.34 3.50	6	158	3.792	5.226	25.979	74.021	1.522
		9	169	5.325				
		8	122	6.557				
7b	1.25 2.50 3.60	18	281	6.405	7.677	38.163	61.837	1.986
		25	343	7.288				
		48	514	9.338				
7c	1.30 2.52 3.93	34	510	6.666	8.221	38.253	61.74	2.091
		40	341	8.797				
		45	489	9.202				
7d	1.17 2.35 3.52	6	158	5.555	4.133	19.232	80.767	1.452
		9	169	5.194				
		4	122	7.633				
7e	1.19 2.38 3.57	7	126	6.382	6.127	30.408	69.592	1.709
		8	154	8.928				
		10	131	6.159				

4. Conclusion

In conclusion, the new tetralone acid analogues of podophyllotoxin (**7a-e**) were synthesized in good yields following Gensler's method with some changes in reagents and reaction conditions. The structures of synthesized compounds were confirmed and characterized by analytical data's such as IR, ¹H NMR, ¹³C NMR, Mass spectra and elemental analysis. They were screened for antimitotic activity. The novel tetralone acids analogues of podophyllotoxin were synthesized by replacing methylene dioxy group in podophyllotoxin with methoxy, methyl, thiomethyl group and hydrogen and fluorine and the trimethoxyphenyl ring with cyclohexyl and lactone ring with carboxylic acid to study the structure activity relationship. It is noteworthy that compound **7b** possessed good antimitotic activity, **7c** and **7e** showed considerable activity and remaining **7a** and **7d** possessed low activity.

5. Acknowledgement

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