The Pharmacological Properties Of Terpenoids From Sandoricum Koetjape

Corresponding Author:
Dr. Amin Malik Shah Abdul Majid,
Lecturer in Universiti Sains Malaysia, Department of Pharmacology, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Minden 11800, Pulau Penang, Malaysia, 11800 - Malaysia

Submitting Author:
Mr. Zeyad D Nassar,
Master Student, Department of Pharmacology, School of Pharmacy, University Sains Malaysia, School of Pharmaceutical Sciences, USM, 11800 - Malaysia

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The Pharmacological Properties Of Terpenoids From Sandoricum Koetjape

**Author(s):** Nassar Z, Aisha A, Abdul Majid A

### Abstract

*Sandoricum koetjape* is a traditional plant belonging to the family of Meliaceae. It is native to Southeast Asian countries, including Malaysia and Philippines. In Malaysia, it is locally known as Santol. The tree is a medium-sized with edible fruit. In Malaysia, the aqueous extract of the bark is traditionally consumed as a tonic after giving birth. Number of comprehensive studies on its phytochemical and pharmacological properties has been reported. Various bioactive compounds have been isolated from fruits, seeds, leaves and bark. More than 10 terpenoids have been isolated and studied for their potential medicinal properties. Terpenoids represent the largest class of secondary metabolites from the natural source. This article aims to review the pharmacological properties of the isolated terpenoids from *Sandoricum koetjape*.

### Review

#### Influence of medicinal plants on diseases treatment:

Plants have formed the basis of sophisticated traditional medicine systems that have been in existence for thousands of years [1]. Plants have been utilized to heal ailments from alleviating headache to treating heart diseases [2].

The first illustrated book about gathering, preparation and use of medicinal plants was written by Chinese Emperor Shen Nung before 3000 thousand years [1]. The Greeks also contributed in the development of the herbal drugs. “De Materia Medica” written by Dioscorides, the Greek physican (100 A.D.), described more than 600 medicinal plants [2]. The expertises of Greeks in herbal medicine were preserved only by Arabs, during the dark and middle Ages. Arabs developed this science using their own resources and together with Greco-Roman, Chinese and Indian herbs [1].

The shift from using ordinary herbal medicines to modern pharmaceuticals was just started in 1800s. This transfer was due starting isolation of pure compounds from plants. In 1805, morphine was purified from the opium. Following the isolation of salicylic acid from the bark of the willow tree, Hoffmann synthesized aspirin in 1897. Ephedrine was isolated from the Chinese herb mahuang (Ephedra) in 1887. The antimalarial drug artemisinin was developed in 1972 from the Chinese herb qinghao (sweet wormwood, Artemisia annua L.) [3].

Although, humans depend on plants from thousands years, the science of medicinal plants is still a vastly unknown. Scholars estimate that 5 % of 250000 species of plants have been investigated [2]. This fact points in the importance of screen new plants for their pharmacological properties.

#### Natural products and cancer treatment:

Some secondary metabolites of the plants such as alkaloids, terpenoids and glycosides serve either as protective agents against various pathogens (e.g. insects, fungi or bacteria) or growth regulatory molecules (e.g. hormone-like substances), as a result, secondary metabolites can serve as potential anticancer drugs, either by direct cytotoxic activity against cancer cells or by modulating the tumor development process [4]. In fact, natural products are considered as a mainstay in cancer treatment, as 60% of worldwide anticancer drugs between 1983 and 1994 were from natural origin [5].

The most famous examples are vinblastine and vincristine from Catharanthus roseus, paclitaxel from Taxus brevifolia Nutt, etoposide and teniposide which are epimers of podophyllotoxin which isolated from roots of various species of the genus podophyllum, and camptothecin which isolated from the Chinese tree Camptotheca acuminata [6]. The impact of these products in cancer treatment is very obvious, paclitaxel and camptothecin were estimated to account for nearly one-third of the global anticancer market or about $3 billion of $9 billion in total annually in 2002 [7].

#### Terpenoids:

Terpenoids are defined as secondary metabolites with molecular structures containing carbon backbones made up of isoprene (2-methylbuta- 1, 3-diene) units. Isoprene contains five carbon atoms and as a result, the number of carbon atoms in any terpenoids is a multiple of five. The terpenoids consists of two isoprene units, i.e. ten carbon atoms. The classification of terpenoids based on the number of isoprene units [8] (Table 1).
More than 36000 terpenoids compounds have been identified, making terpenoids the largest class of plant metabolites. Most of the thousands of terpenoids produced by plants have no discernible role in growth and development and are, therefore, often classified as ‘secondary’ metabolites. Although comparatively few of these substances have been investigated in depth, they are thought to serve primarily in ecological roles, providing defence against and acting as attractants for animals that disperse pollen or seeds or as inhibitors of germination and growth of neighbouring plants [9-11]

The terpenoids group show significant pharmacological activities, such as anti-viral, anti-bacterial, anti-malarial, anti-inflammatory, inhibition of cholesterol synthesis and anti-cancer activities [12].

**Sandoricum koetjape:**

S. koetjape is traditional medicinal plant belonging to the family Meliaceae, it is native to Malaysia, Cambodia and Southern Laos. It has been introduced into the Philippines, India, Indonesia, and Andaman Islands since long time ago. A few samples were introduced into North and South America such as Honduras and Costa Rica, and Miami and Florida in USA [13].

S. koetjape is an evergreen tree grows 15-45 m tall in fast manner, as the plant gets older the trunk get buttressed and branched close to the ground. Younger branches have dense brown hair. The 3 leaflets leaves are compound, elliptic to oblong-ovate, 20-25 cm long, blunt at the base and pointed at the apex. The flowers are 1 cm long consist of 5 petals stalked panicles 15-30 cm in length, and have green, yellow, or pinkish-yellow colour Plate 1.1 shows picture of leaves. The leaves, seeds and fruits of S. koetjape.

There are two types of S. koetjape fruit, viz, red or yellow. The rind of the former type is sour, have thicker rind and the amount of pulp is less. While the yellow fruits are sweet, have thin rind and a thicker pulp. However, nowadays only the yellow variety is available in Malaysia [13,14].

In Malaysia, S. koetjape is known as sentieh, sentol, setol, sentul, setul, setui, kechapi or ketapi. The traditional Indonesian names are ketjapi or sentool. While in Thailand it is called saton, satawn, katon, or ka-thon [13,14].

The classification of S. koetjape is demonstrated in table 2.

**Traditional medicinal uses of S. koetjape:**

In Malaysia, the aqueous extract of the bark is traditionally consumed as a tonic after giving birth [15], while in Indonesia it is used by folk medical practitioners to treat leucorrhoea and colic with the decoction prepared from the bark of the plant [16].

Phytochemistry and pharmacological activities of S. koetjape:

The seeds, leaves, fruits and the stem bark of S. koetjape have been rigorously studied for the chemical constituents. Various S. koetjape's extracts and many isolated chemicals showed potential pharmacological activities.

Andirobin-type limonoids have been isolated from S. koetjape’s seeds, namely sandoricin and 6-hydroxysandoricin. These limonoids showed remarkable anti-feedant activities [17].

Bryononic acid and bryonolic acid terpenoids and meso-inositol and dimethyl mucate polyalcohol have been isolated from the S. koetjape’s fruits hulls [18].

The leaves have been yielded trijugin limonoids namely Sandrapins A, B, C, D and E, and sandoripin A and B [19].

Several comprehensive studies have been carried out on the stem bark. A number of triterpenoids have been isolated from the stem bark such as, katonic acid, indicic acid [20], koetjapic acid, 3-oxo-12-oleanen-29-oic acid, alloanomadendrene, caryophyline oxide, spathulenol [21], bryononic acid, secobryononic acid, secoisobryononic acid [22], 20-epikoetjapic acid, 3-epikatonic acid and sandorinic acid A, B and C [23]. Figure 1.3 shows chemical structure of some terpenoids extracted from the bark.

Many pharmacological properties have been investigated for the majority of the isolated terpenoids. The cytotoxic properties of Koetjapic acid, Katonic acid and 3-oxo-12-oleanen-29-oic acid were investigated against ten cancer cell lines. Katonic acid and 3-oxo-12-oleanen-29-oic were cytotoxic against many of cancer cell lines (i.e. IC50 < 20 µg/ml), they were very potent against murine lymphocytic leukaemia P-388 cell line (IC50 = 0.11 and 0.61 µg/ml respectively). In contrast, koetjapic acid was inactive against all of tested cancer cell lines [21].

Although koetjapic acid has not been reported as a cytotoxic compound till now, it showed notable DNA polymerase inhibition activity [24]. Ismail et al., reported ichthyotoxic properties of koetjapic acid and 3-oxo-12-oleanen-29-oic acid [25]. However, katonic acid has not exhibited significant ichthyotoxic activity. In the same study, all three terpenoids was considered as anti-tumor promoting agents as they show significant inhibitory effect on induced-Epstein-Barr virus early antigen activation. Koetjapic acid was the most potent agents among the three terpenoids in the lastest two mentioned assays (Ichthyotoxicity and anti-tumor promotion studies). Koetjapic acid also appears to be a promising cancer chemoprevintive compound, as it remarkably delayed
tumor promotion in two stage mouse carcinogenesis induced by 7,12 dimethylbenz(a)anthracin and promoted by 12-O-tetradecanoylphorbol 13-aceate (TBA) [25].

In TBA-induced mouse ear odema assay to explore the anti-inflammatory properties, methanolic extract, o xo-12-oleanen-29-oic acid, Katonic acid and Koetjapic acid inhibits inflammation by 94 % 94 %, 81 % and 13 % respectively [26]. Koetjapic acid also inhibited the growth of Staphylococcus aureus, methicillin-resistant S. aureus and Pseudomonas aeruginosa, with MIC range of 3.125-6.25 µg/ml [27]. Recently, hexan extract of S.koetjape shows noteworthy anti-angiogenic activity in a study depended on ex-vivo rat aortic ring assay. Hexan extract also shows selective cytotoxicity against colorectal carcinoma HCT 116 cell line. The apoptotic propoties of S.koetjape hexan extarct have been confirmed on two cancer cell lines, MCF-7 and HCT 116 [28,29].

Koetjapic acid which is the main compound in S. koetjape was isolated successfully with simple non-chromotgraphic method with high percentage yeild (Table 3). The remarkaple pharmacological activity make this compound as good candidite as a drug, however, a comprehinsive toxicity study has to be carried out. Besides, it is very critical to find a solution of poor solubility of it as well as its bioavailabilty.

Acknowledgement(s)

Zeyad D. Nassar and A.F.A. Aisha would like to acknowledge USM for the USM Fellowship.
This work was financially supported by Universiti Sains Malaysia (USM) Research University Grant [Grant 1001/PFARMASI/81144].

References

Illustrations

Illustration 1

Table 1 The classification of Sandricum koetjape

<table>
<thead>
<tr>
<th>Class</th>
<th>Magnoliopsida, Dicotyledons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subclass</td>
<td>Rosidae</td>
</tr>
<tr>
<td>Order</td>
<td>Rutales</td>
</tr>
<tr>
<td>Suborder</td>
<td>Meliineae</td>
</tr>
<tr>
<td>Family</td>
<td>Meliaceae</td>
</tr>
<tr>
<td>Genus</td>
<td>Sandoricum</td>
</tr>
<tr>
<td>Specific epithet</td>
<td>koetjape Merr.</td>
</tr>
<tr>
<td>Botanical name</td>
<td><em>Sandoricum koetjape</em></td>
</tr>
<tr>
<td>Synonyms</td>
<td><em>Sandoricum indicum</em> Cav., <em>Sandoricum nervosum</em> Blume, and <em>Melia koetjape</em> Burm. f.[13]</td>
</tr>
</tbody>
</table>
Illustration 2

Table 2 The nomenclature of terpenoids.

<table>
<thead>
<tr>
<th>Name</th>
<th>No. of isoprene units</th>
<th>No. of carbon atoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemiterpenoids</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Monoterpenoids</td>
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<td>10</td>
</tr>
<tr>
<td>Sesquiterpenoids</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Diterpenoids</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Sesterterpenoids</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>Triterpenoids</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>Tetraterpenoids</td>
<td>8</td>
<td>40</td>
</tr>
<tr>
<td>Polyisoprenoids</td>
<td>&gt;8</td>
<td>&gt;40</td>
</tr>
</tbody>
</table>
Illustration 3

Table 3 The percentage yield of koetjapic acid gained by previous studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Percentage yield %</th>
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</thead>
<tbody>
<tr>
<td>Kaneda et al., 1992 [21]</td>
<td>0.11 %</td>
</tr>
<tr>
<td>Tanaka et al., 2001 [23]</td>
<td>0.14%</td>
</tr>
<tr>
<td>Rasadah et al., 2004 [26]</td>
<td>0.0036%</td>
</tr>
<tr>
<td>Ismail et al., 2003 [25]</td>
<td>0.0825%</td>
</tr>
<tr>
<td>Nassar, et al., 2010 [30]</td>
<td>0.2 %</td>
</tr>
</tbody>
</table>
Illustration 4

Figure 1 Pictures of leaves, seeds and fruits of S.koetjape
Illustration 5

Figure 2 Chemical structures of triterpene isolated from S. koetjape
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Reviews

Review 1

Review Title: The Pharmacological Properties Of Terpenoids From Sandoricum Koetjape

Posted by Dr. Malek Alzhihlif on 21 Jan 2011 10:33:08 PM GMT

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<td>Is the subject of the article within the scope of the subject category?</td>
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<tr>
<td>2</td>
<td>Are the interpretations / conclusions sound and justified by the data?</td>
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<td>3</td>
<td>Is this a new and original contribution?</td>
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<td>4</td>
<td>Does this paper exemplify an awareness of other research on the topic?</td>
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<td>Are structure and length satisfactory?</td>
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<td>6</td>
<td>Can you suggest brief additions or amendments or an introductory statement that will increase the value of this paper for an international audience?</td>
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<td>7</td>
<td>Can you suggest any reductions in the paper, or deletions of parts?</td>
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<td>8</td>
<td>Is the quality of the diction satisfactory?</td>
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<tr>
<td>9</td>
<td>Are the illustrations and tables necessary and acceptable?</td>
</tr>
<tr>
<td>10</td>
<td>Are the references adequate and are they all necessary?</td>
</tr>
<tr>
<td>11</td>
<td>Are the keywords and abstract or summary informative?</td>
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</tbody>
</table>

Rating: 8

Comment:
The “Influence of medicinal plants on diseases treatment” section can be written in more concise way and I think the title does not reflect what is really discussed by the author

From my opinion the author need to introduce more information regarding the mechanism of action in the malignant cell especially the DNA polymerase inhibition story.

One attractive point mentioned in this review is the anti-bacterial activity and more information and scientific finding will add a better value for the review.

Competing interests: no

Invited by the author to make a review on this article? : Yes

Experience and credentials in the specific area of science:
i have been working on plant extracts activity against cancer for a while and some publications will come out soon

Publications in the same or a related area of science: No

How to cite: Alzhihlif M. The Pharmacological Properties Of Terpenoids From Sandoricum Koetjape [Review of the article 'The Pharmacological Properties Of Terpenoids From Sandoricum Koetjape ' by ]. WebmedCentral 1970;2(1):REVIEW_REF_NUM399
Review 2

Review Title: The pharmacological properties of terpenoids from 'Sandronicum koetjape'

Posted by Prof. Marcello Iriti on 16 Dec 2010 03:52:22 AM GMT

1. Is the subject of the article within the scope of the subject category? Yes
2. Are the interpretations / conclusions sound and justified by the data? Yes
3. Is this a new and original contribution? Yes
4. Does this paper exemplify an awareness of other research on the topic? Yes
5. Are structure and length satisfactory? Yes
6. Can you suggest brief additions or amendments or an introductory statement that will increase the value of this paper for an international audience? Yes
7. Can you suggest any reductions in the paper, or deletions of parts? No
8. Is the quality of the diction satisfactory? No
9. Are the illustrations and tables necessary and acceptable? Yes
10. Are the references adequate and are they all necessary? Yes
11. Are the keywords and abstract or summary informative? Yes

Rating: 5

Comment:
According to my opinion, the manuscript represents a satisfactory review on the pharmacological activities of Sandoricum koetjape. However, I suggest some modifications:

1. pg 2, 'Natural products and cancer treatment', the authors should better specify the ecological role of secondary metabolites (for plant), in opposition to their biological activities relevant to human health ('as a result' is misleading). Furthermore, I would add phenylpropanoids to the list of secondary metabolites.

2. I would introduce a review on limonoids, because of their abundance in S. koetjape, such as that of Roy and Saraf 2006, Limonoids, overview of significant bioactive triterpenes distributed in plants kingdom, Biol Pharm Bull, as well as the reference Panchaoren et al., 2009, Two new limonoids from the leaves of Sandoricum koetjape, Nar Prod Res 23(1):10-16.

3. A number of typing and diction errors are present in the text, particularly in pg 4 and also in References.

4. Tables 1 and 2 have been exchanged; in tab 1 (that should be the tab 2) there is 'Sandricum' and in tab 2 (that should be the tab 1) there is 'triterpenoids'.

5. In the text, fig. 1 and 2 should be reported, instead of 'Plate 1.1' and 'Figure 1.3' (pg 3)

6. The acronym MIC (minimum inhibitory concentration) should be written in extenso

Competing interests: no

Invited by the author to make a review on this article? : No

Experience and credentials in the specific area of science:
Biological activity of grape chemicals

Publications in the same or a related area of science: Yes


How to cite: Iriti M. The pharmacological properties of terpenoids from 'Sandronicum koetjape'[Review of the article 'The Pharmacological Properties Of Terpenoids From Sandoricum Koetjape ' by ].WebmedCentral
Review 3

Review Title: Sandoricum Koetjape

Posted by Mr. Suchir Arora on 12 Dec 2010 12:04:11 PM GMT

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<tr>
<td>11</td>
<td>Are the keywords and abstract or summary informative?</td>
<td>Yes</td>
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</tbody>
</table>

Rating: 8

Comment:
General comment on referring some patents as well.... there are many of them focussed on Terpenoids

Competing interests: None

Invited by the author to make a review on this article? : Yes

Experience and credentials in the specific area of science:
Yes

Publications in the same or a related area of science: No

How to cite: Arora S. Sandoricum Koetjape[Review of the article 'The Pharmacological Properties Of Terpenoids From Sandoricum Koetjape ' by ].WebmedCentral 1970;1(12):REVIEW_REF_NUM236
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