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# An *in silico* Approach to Predict Toxicological Mechanisms of Selected Phytochemicals from Areal Parts of *Heliotropium indicum* Linnaeus and Synthetic Medicines

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**Abstract:** ***This in silico study was attempted to predict toxicological mechanisms of selected phytochemicals of Hatisur weed (Heliotropium indicum Linnaeus) and synthetic medicines used for anti-inflammation. we used the ProTox-II online tool (version, 3.0) for the prediction of toxicological mechanisms especially Tox21-Nuclear receptor signalling pathways and -stress response pathways of selected phytochemicals and synthetic medicines. In the present study, for Tox-21 nuclear signalling pathways and Tox-21 stress response pathways, all the compounds were found inactive on the different parameters. In conclusion, all of these phytochemicals and synthetic medicines obtained inactive for Tox-21 nuclear signalling pathways and Tox-21 stress response pathways. It is suggested to conduct in vivo bioassay to validate these predictive results in future.***

**Keywords:** *Heliotropium indicum* Linnaeus, I*n silico* study, Phytochemicals, Synthetic medicines, Toxicological mechanisms

## 1. Introduction

Generally, chronic joint inflammatory disorders are osteoarthritis (OA) and rheumatoid arthritis (RA) found with an increase of inflammation, pain, and oxidative stress, resulting in progressive histological alterations and disabling symptoms. [1]

In recent days, research on phytomedicines concerns preventing inflammation and pain without any side effects. [2-4] Many synthetic drugs pose side effects. [5, 6] In this context, natural products derived from plants may be less expensive, indigenous, etc. and can be used in new drug discovery.

Some earlier studies described the medicinal importance of this weed (*Heliotropium indicum* Linnaeus) and few phytochemicals are predicted non-toxic. [4, 7] Moreover, this medicinal weed has phytochemicals to prevent many disorders such as inflammation, pain, nociceptive activity, etc. [2, 4-6] But some studies reported that solvent extract of plant parts may contain allelochemicals that cause allelopathy and toxicity to animals. [8, 9]

In this context, toxicity screenings especially *in vitro* and *in vivo* assay of each phytochemical is costly, long-duration of experimentation and require animal sacrifice. Whereas *in silico* prediction helps faster screening, no animal harming and inexpensive procedure. [10, 11] The past to recent research, many reports revealed that *in silico* toxicity prediction of natural and synthetic compounds for new drug design is an easy procedure. [11-14]

This study was attempted to predict toxicological mechanisms of selected phytochemicals of Hatisur weed (*Heliotropium indicum* Linnaeus) and synthetic medicines used for anti-inflammation.

## 2. Materials and Methods

As per our earlier study, we considered all established phytochemicals of *Heliotropium indicum* Linnaeus and synthetic medicines viz. Indomethacin and Ibuprofen. [7]

In this study, we used the ProTox-II online tool (version, 3.0) as per the development by Drwal et al. [15] and Banerjee et al. [16] for the prediction of toxicological mechanisms especially Tox21-Nuclear receptor signalling pathways and -stress response pathways of selected phytochemicals and synthetic medicines. As per earlier study by Mishra and Talapatra, [17] we considered different parameters of toxicological mechanisms.

## 3. Results

Table 1 predicts the results of selected phytochemicals and synthetic medicines on the activity or inactivity of Tox-21 nuclear signalling pathways. All the compounds were found inactive on the different parameters.

Table 2 predicts the results of selected phytochemicals and synthetic medicines on the activity or inactivity of Tox-21 stress response pathways. All the compounds were found inactive on the different parameters.

**Table 1:** Prediction of Tox21-Nuclear receptor signalling pathways of phytochemicals of areal parts of *H. indicum* and synthetic medicines

| Sl. No. | Compounds name | Ahr | P (%) | AR | P (%) | AR-LBD | P (%) | Ar | P (%) | ER | P (%) | ER-LBD | P (%) | PPAR-Gamma | P (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Phytochemicals** | | | | | | | | | | | | | | | |
| 1. | Heleurine | In | 94.0 | In | 94.0 | In | 96.0 | In | 89.0 | In | 91.0 | In | 96.0 | In | 97.0 |
| 2. | Echinatine | In | 97.0 | In | 96.0 | In | 97.0 | In | 87.0 | In | 86.0 | In | 96.0 | In | 98.0 |
| 3. | Heliotrine | In | 96.0 | In | 95.0 | In | 97.0 | In | 85.0 | In | 87.0 | In | 97.0 | In | 98.0 |
| 4. | Heliotridine | In | 96.0 | In | 96.0 | In | 98.0 | In | 96.0 | In | 85.0 | In | 98.0 | In | 99.0 |
| 5. | Indicine | In | 97.0 | In | 96.0 | In | 97.0 | In | 87.0 | In | 86.0 | In | 96.0 | In | 98.0 |
| 6. | Indicine N-oxide | In | 96.0 | In | 95.0 | In | 96.0 | In | 90.0 | In | 84.0 | In | 95.0 | In | 98.0 |
| 7. | Lasiocarpine | In | 95.0 | In | 95.0 | In | 97.0 | In | 88.0 | In | 89.0 | In | 97.0 | In | 98.0 |
| 8. | Trachelanthamidine | In | 96.0 | In | 96.0 | In | 99.0 | In | 96.0 | In | 94.0 | In | 99.0 | In | 99.0 |
| 9. | Retronecine | In | 96.0 | In | 96.0 | In | 98.0 | In | 96.0 | In | 85.0 | In | 98.0 | In | 99.0 |
| 10. | Supinine | In | 95.0 | In | 94.0 | In | 97.0 | In | 91.0 | In | 90.0 | In | 94.0 | In | 97.0 |
| 11. | β-Linalool | In | 100.0 | In | 100.0 | In | 100.0 | In | 99.0 | In | 99.0 | In | 99.0 | In | 100.0 |
| **Synthetic medicines** | | | | | | | | | | | | | | | |
| 1. | Indomethacin | In | 88.0 | In | 99.0 | In | 99.0 | In | 96.0 | In | 96.0 | In | 97.0 | In | 100.0 |
| 2. | Ibuprofen | In | 99.0 | In | 100.0 | In | 100.0 | In | 99.0 | In | 90.0 | In | 99.0 | In | 99.0 |

AhR = Aryl hydrocarbon Receptor; AR = Androgen Receptor; AR-LBD = Androgen Receptor Ligand Binding Domain; Ar = Aromatase; ER = Estrogen Receptor Alpha; ER-LBD = Estrogen Receptor Ligand Binding Domain; PPAR-Gamma = Peroxisome Proliferator Activated Receptor Gamma; In = Inactive; Ac = Active; P = Probability

**Table 2:** Prediction of Tox21-Stress response pathways of phytochemicals of areal parts of *H. indicum* and synthetic medicines

| Sl. No. | Compounds name | nrf2/ARE | P (%) | HSE | P (%) | MMP | P (%) | p53 | P (%) | ER | P (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Phytochemicals** | | | | | | | | | | | |
| 1. | Heleurine | In | 87.0 | In | 87.0 | In | 90.0 | In | 91.0 | In | 96.0 |
| 2. | Echinatine | In | 94.0 | In | 94.0 | In | 93.0 | In | 88.0 | In | 96.0 |
| 3. | Heliotrine | In | 93.0 | In | 93.0 | In | 91.0 | In | 87.0 | In | 96.0 |
| 4. | Heliotridine | In | 96.0 | In | 96.0 | In | 94.0 | In | 96.0 | In | 97.0 |
| 5. | Indicine | In | 94.0 | In | 94.0 | In | 93.0 | In | 88.0 | In | 96.0 |
| 6. | Indicine N-oxide | In | 92.0 | In | 92.0 | In | 93.0 | In | 90.0 | In | 96.0 |
| 7. | Lasiocarpine | In | 91.0 | In | 91.0 | In | 92.0 | In | 88.0 | In | 96.0 |
| 8. | Trachelanthamidine | In | 98.0 | In | 98.0 | In | 93.0 | In | 96.0 | In | 98.0 |
| 9. | Retronecine | In | 96.0 | In | 96.0 | In | 94.0 | In | 96.0 | In | 97.0 |
| 10. | Supinine | In | 89.0 | In | 89.0 | In | 92.0 | In | 91.0 | In | 96.0 |
| 11. | β-Linalool | In | 99.0 | In | 99.0 | In | 86.0 | In | 100.0 | In | 100.0 |
| **Synthetic medicines** | | | | | | | | | | | |
| 1. | Indomethacin | In | 98.0 | In | 98.0 | In | 88.0 | In | 95.0 | In | 99.0 |
| 2. | Ibuprofen | In | 99.0 | In | 99.0 | In | 96.0 | In | 99.0 | In | 99.0 |

nrf2/ARE = Nuclear factor (erythroid-derived 2) -like 2/antioxidant; HSE = Heat shock factor response element; MMP = Mitochondrial Membrane Potential; p53 = Phosphoprotein (Tumor Supressor); ATAD5 = ATPase family AAA domain-containing protein 5; In = Inactive; Ac = Active; P = Probability

## 4. Discussion

The phytochemicals Heliotridine, Retronecine and β-Linalool were predicted class V, may be harmful if swallowed in rat models as median lethal dose of 3500.0 mg/kg and 2200 mg/kg, respectively. [7]

In the present study, for Tox-21 nuclear signalling pathways and Tox-21 stress response pathways, all the compounds were found inactive on the different parameters. Interestingly, Tox-21 assessment is very much helpful as per *in vitro* quantitative high-throughput screening (qHTS) tests for toxicological evaluation of botanical and dietary supplements as per the study by Hubbard et al. [20] Moreover, Tox21 is made up of dataset >10, 000 compounds that consisting of 12 types of *in vitro* tests in which 7 types of parameters for the nuclear receptor signalling pathways and 5 types of the parameters for the stress response (SR) pathway. [21]

Likewise, these phytochemicals especially Heliotridine, Retronecine and β-Linalool could be suitable leads for new drug design after derived from H. indicuam because this plant serve as medicinal properties especially for anti-inflammation. [22]

## 5. Conclusion

It is concluded that all of these phytochemicals obtained inactive for Tox-21 nuclear signalling pathways and Tox-21 stress response pathways when compared to Indomethacin and Ibuprofen like synthetic medicines. In future study, it is suggested to conduct *in vivo* bioassay to validate these predictive results.

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**Conflict of interest**
It is declared none.

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