Systematic Evaluation of natural compounds: Trachyspermum Ammi and Colchicum Luteum to identify targets of Rheumatoid Arthritis

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Abstract

Rheumatoid Arthritis is a persistent sickness affecting 0.5 – 1% of the population. Rheumatoid is more normal among females. It is an autoimmune illness and there is no complete treatment for the disease yet. The current treatment of Rheumatoid Arthritis includes NSAIDs, DMARDs, Glucocorticoids, and Biologics that suppress the prognosis and symptoms of the disease but do not treat the disease. Trachyspermum Ammi and Colchicum Luteum are the medicinal plants reported to exhibit antioxidant action. The dynamics of phytochemicals of these plants can be used for the treatment of Rheumatoid Arthritis by inhibiting various pathways that upgrade the immune response. The shortlisted phytochemicals of both the plants demonstrated drug likeliness property. The in-silico docking examination of shortlisted phytochemicals and medications that are prescribed to RA patients is done. The docking results showed different phytochemicals binding on the reported RA targets having greater binding affinity as compared to available drugs. This examination presumes that the shortlisted dynamic phytochemicals having better binding energies and have less side-effects as the phytochemicals are derived from medicinal plants due to which could be considered for future research when contrasted with the commercial drugs accessible for Rheumatoid Arthritis.

Keywords: In-silico, Rheumatoid Arthritis, Trachyspermum Ammi, Colchicum Luteum, Docking

1. Introduction

Rheumatoid arthritis is an autoimmune disease associated with progressive inflammation of joints. It is considered as a very important cause of disabilities. Initially, rheumatoid arthritis affects small joints in arms and legs but the inflammation progress and affects synovial tissues (Firestein, 2003). It affects 0.5 – 1% of the population around the world (Marra et al., 2011).

Increase in the mortality rate of Rheumatoid Arthritis has been reported. The main reason behind this increase is the number of comorbidities linked to the disease and also the presence of the Rheumatoid Factor has seen to be another cause of increases in the mortality gap among the patients of RA (Myasoedova et al., 2010). There is no evidence to whether the survival has improved. Some studies have shown to have the improved mortality rate over the years. This could be the because of the early diagnosis of RA and the new advance medication (Gonzalez et al., 2007)

From various studies the higher prevalence among females is seen irrespective of the demographics by two folds as compared to male. Males have approximately 1.7% and females have 3.6% of the chance of developing RA during the course of their life (Crowson et al., 2011) and both the environmental and genetic factors contribute their role in the occurrence of the disease (Alamanos et al., 2005).

The exact cause of RA is unknown. But many factors are reported to play role e.g. sex, age, gender, ethnicity, hormonal levels, alcohol consumption, weight, smoking and diet. The factors are divided based on environmental and genetic. In most of the cases, pathogenesis or the development is based on both the factors together (Alamanos et al., 2005). Presently the treatment options for Ra includes non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying anti-rheumatic drugs (DMARDs) and biologic (Pincus et al., 1999).

2. Literature Review

Oxidation reduction reaction is important for stable immune system. any imbalance in the reaction leads to the progression in RA. The imbalance is between the pro-oxidative compounds and the anti-oxidative compounds and normally the increase in the reactive oxygen species causes malfunctioning of the immune system (Filippin et al., 2008). It increases the risk of activating pathways that plays an important role in the pathophysiology of RA as discussed earlier. This reaction can be activated in response to drugs, stress, diet, and hormonal imbalances (Phull et al., 2018). In normal conditions, ROS play's role in safeguarding the biological system from the pathogens and also aid in the regeneration but when the functioning alters it can cause many diseases e.g., neurodegenerative, inflammatory disease and even cardiovascular (Abbas & Monireh, 2008). The reactive oxygen and nitrogen species are collectively involved in ROS. One is the secondary messenger while the other is a pathologic mediator further having two classification i.e., radicals (Superoxide, Hydroxyl Radical and NO), and Non-radicals (Hydrogen peroxide) (Griffiths, 2005). ROS in general play's its role as a secondary messenger to activate the genes that are related to the inflammatory response (Kohchi et al., 2009). It was initially reported that ROS activates NF-κB which is responsible for activating Tumor Necrosis Factor- alpha (TNF- α) and Interleukin 1 Beta (IL-1β) further activating the inflammatory cascade (Li et al., 2018).

This redox reaction activation eventually leads to apoptosis of cells. In mouse models the ROS reaction was manipulated which reported the role of ROS in RA leading to a complex inflammatory process which consists of various pro-inflammatory cytokines and signaling pathway playing an important role in the progression of the disease (Filippin et al., 2008).

3. Methodology

Leaves of the plant T. Ammi and C. Luteum were obtained. Oxidation and phytochemical analysis was conducted to check the presence of phytochemicals in the extract. Further in-silico analysis was conducted to identify the drug likeliness of the compounds present in both the plants based on Lipinski rule of 5 and their ADMET properties. Further a protein-protein interaction map were constructed of both the plants and RA protein targets. This gave the information regarding the potential target genes that were further subjected to the docking analysis The commercial drugs were searched for the

same targets that were found similar in the plants and in the development of RA disease and comparative docking analysis was done.

4. Results

9 phytochemicals from each plant were shortlisted that were found have drug likeliness. The docking results of the phytochemicals and the commercial drugs targeting the proteins that are involved in the pathogenesis or the development of RA is presented in the following table. Many compounds like 3,4-bis(4-hydroxyphenyl)-3,4-hexanediol, Benzoic acid, 2-hydroxy-5-(4-methyl-1-piperazinyl)methyl-, methyl ester, 3,3'-Isopropylidenebis(1,5,8,11-tetraoxacyclotridecane), 2,4a,7-Trihydroxy-1-methyl-8-methylenegibb-3-ene 1,10-carboxylic acid 1-4 lactone and Topotecan showed better binding affinities as compared to the drugs for the specified targets.

Target (SYL)	Phytochemicals of C. Luteum Drug	S- Value	RMSD
JAK 1	Ethyl iso-allocholat	-8.01	1.13
	Upadacitinib	-12.3	1.61
JAK 2	3,4-bis(4-hydroxyphenyl)- 3,4-hexanediol	-12.63	10.80
	Barcitinib	-5.25	1.22
JAK 3	Topotecan	-14.24	1.35
	Tofacitinib	-10.3	0.95
PTGS1	3,4-bis(4-hydroxyphenyl)- 3,4-hexanediol	-12.05	1.2
	Dinoprostone	-11.4	1.1
PTGS2	3,4-bis(4-hydroxyphenyl)- 3,4-hexanediol	-12.9334	1.3
	Celecoxib	-8.4	2.0
CASP1	Cyclohexanone, 3-carbomethoxy-4-(2'-carbomethoxyvinyl)-4-hydroxy-, TMS derivative	-7.08	3.26
	Pralnacasan	-6.8	2.1
MMP	Topotecan	-9.02	2.15
	Regorafenib	-9.5	1.9

Targets	Phytochemicals of T. Ammi Drugs	S-Value	RMSD
JAK 1	Benzoic acid, 2-hydroxy-5-(4-methyl-1-piperazinyl)methyl-, methyl ester	-13.364	01.87
	Upadacitinib	-12.15	1.61
JAK 2	3,3'-Isopropylidenebis(1,5,8,11-tetraoxacyclotridecane)	-17.2966	0.9
	Barcitinib	-5.25	1.22
JAK3	2,4a,7-Trihydroxy-1-methyl-8-methylenegibb-3-ene 1,10-carboxylic acid 1-4 lactone	-16.5164	1.9
	Tofacitinib	-10.3	0.95

PTGS2	4(3H)-Quinazolone, 3-[2-hydroxy-3-(2-oxo-3-propyloxazolidin-4-yl)propyl]-	-9.5	2.2
	Celecoxib	-8.4	2.0
PTGS1	2,4a,7-Trihydroxy-1-methyl-8-methylenegibb-3-ene 1,10-carboxylic acid 1-4 lactone	-10.260	2.05
	Dinoprostone	-11.4	1.1
CASP1	3,3'-Isopropylidenebis(1,5,8,11-tetraoxacyclotridecane)	-7.407	2.3
	Pralnacasan	-6.8	2.1

5. Conclusion

The phytochemicals and the common targets among plants, RA disease and commercial drugs were retrieved using the relevant data bases and literature. On performing the docking analysis, the energy values collected showed a significant differences in the comparative docking regarding the affinity of binding of the proposed compound that can be used as a drug as compared to the available commercial drug. More research needs to be done to understand the biological and molecular mechanisms by conducting the in-vitro and in-vivo analysis. The commercial drugs have reported to show various side effects but these proposed compounds are extracted from the plant possessing less toxicity and side effects.

6. References

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