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PHYTOCHEMICALS AS BIOMARKER MODULATORS IN RHEUMATOID ARTHRITIS: A STEP TOWARDS ADVANCING PERSONALIZED HERBAL MEDICINE

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ABSTRACT

A personalized medicine is a contemporary form of medicine focusing on a combination of genetic, metabolic and clinical information to help predict the risk of diseases thus preventing illness early and treating them in a very personalized manner. Personalized approaches have been shown to act as a way of enhancing diagnosis, treatment and management in rheumatoid arthritis (RA), a chronic autoimmune disease that is seen in 1 out of 100 adults. It is a disease that causes immune-mediated inflammation of the synovial membrane which causes cartilage and bone destruction. The application of traditional treatment varies because of the clinical characteristics of age, sex, smoking, BMI and adherence to medications. The improvement of omics technologies including genomics, transcriptomics, proteomics, metabolomics and epigenetics has improved the knowledge of RA pathogenesis and made the discovery of biomarkers to optimize therapy easier. Pharmacogenomics determines genetic changes that affect the reaction to drugs whereas metabolomics and proteomics identify biochemical and protein changes associated with the disease activity. Multi-omics and clinical information are further combined with artificial intelligence (AI) and machine learning (ML) to forecast responses to treatments and optimize personalized care. TNF- alpha, IL-1, IL-6 and IL-17 are biomarkers that are important in the process of inflammation and are used as a form of therapy. In general, personalized medicine of RA is a predictive, preventive, personalized and participatory model which improves the treatment outcomes, reduces the adverse effects and improves precision medicine in case of autoimmune diseases.

KEYWORDS: Personalized medicine, Rheumatoid arthritis, Biomarkers, Pharmacogenomics, Omics technologies, Artificial intelligence, cytokine.

INTRODUCTION

A contemporary medical approach called "Personalized medicine" combines a patient's genetic, metabolic and clinical data to predict illness risk before symptoms manifest. It focus on early prevention and intervention rather than treating end-stage disease, this method is known as "Personalized medicine," which is an acronym for precaution that not only acknowledges the individualized character of medical strategy but also describes predictive, preventative and participatory approaches.[1,2,3] Prediction is represented by the first "P", by combining genetic information with biomarkers that show how severe a disease is and how it can progress. Personalized medicine can classify individuals into high to low risk groups.[4,5]To enhance prediction, genetic and biomarker data analysis should be evaluated along with other factors like patient lifestyle habits such as smoking, family background of autoimmune disorders, clinical signs, genetic history and lab reports.[4,6] The second "P" stands for prevention which targets to detect people at risk of any preclinical signs that may appear, so that preventive approaches can be applied.[7] The third "P" stands for personalize. Tolstoy wrote, "Happy families are all alike; every unhappy family is unhappy in its own way". Rewriting this concept, while people have a health issue, they often sense different from others and trust that they are not suitable for the average group. This is not only a subjective perspective in fact, every individual is different, comprising how diseases influence them due to variation in genome and external factors.[8] Moreover, a single individual shows variations that influence on how people react to therapy.[7]This difference is clearly seen in Monozygotic twins who often show various response to autoimmune as well as chronic inflammatory disorders, focusing on the role of epigenetic factors.[9] So, each individual should be treated as a unique individual.[10] At last, the Fourth "P" stands for participatory part in personalized medicine, the individual must vigorously take a part in prevention and personalized therapy for it to be more efficient.[11]

Rheumatoid arthritis

Rheumatoid arthritis is a persistent inflammatory disorder that can influence multiple systems and contributes to about 1% of adults.[12] It initiates inflammation of the Synovial joint which can lead to joint deterioration, disability and shortened life span by around five years.[13]

Etiology

The causes of rheumatoid arthritis are yet idiopathic, but there is a proof that the disorder is mediated by the immune system, various factors may trigger the immune response in a genetically predisposed individual. The studies of population reveals that both environmental and gene related factors lead to Rheumatoid arthritis even though the genetic mechanisms of Rheumatoid arthritis were partially understood and possibly salient genetic risk factors is an individual’s Class II MHC haplotype.[14]

Pathophysiology:

Rheumatoid arthritis evolves when various inflammatory cells infiltrate the joint spaces. The disorders are caused by chronic inflammation where antigens trigger the lymphocytes that deposit with in the joint excite most cells and macrophages secrete cytokines like Tissue Necrosis factor- alpha and Interleukin-I (IL-I) which sustain a pro inflammatory network. These mediators trigger the enzymes that degrade the joint matrix, finally leading to tissue damage.[15,16] With prolonged inflammation, the synovial lining expands and develops abnormally, forming pannus that progressively erodes cartilage as well as bone. In an individual with specific genetic backgrounds who are influenced by environmental factors, the intrinsic immune system acts by stimulating dendritic cell macrophages and synoviocytes

then move to lymphoid tissues where they present antigens and stimulate T-cells. These T-cell subsequently triggers the B-cells. Both B-cells and T-cells transit back into the joint where they stimulate osteoclasts and enlist more Inflammatory Cells. The secretion of proteolytic enzymes causes degenerative destruction of bone, cartilage and other joints.[14]

Diagnosis

For the diagnosis of Rheumatoid arthritis, the European League of Rheumatology improved their management of rheumatoid arthritis guidelines in 2019.[17] According to the criteria, when Inflammation along with swelling is identified in at least single or multiple Joints; the following four items are validated:

a. Number of symptomatic joints
b. Rheumatoid factor (RF) or Anti cyclic citrullinated peptide antibody (ACPA)
c. C-reactive protein (CRP), erythrocyte sedimentation rate [ESR]
d. Duration of symptoms.

Rheumatoid arthritis is examined and treatment with anti-rheumatic drugs is initiated. However, as no condition other than Rheumatoid arthritis may induce the total score to be six or more, it is essential to thoroughly diagnose whether other disorders are present prior to scoring.[18] Adequately managing therapy requires accurate monitoring to keep disorder activity controlled under distinct conditions. At present, the most reliable way to analyze this is through complete disorder activity Criteria, such as the Disease Activity score (DAS), Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI). These tools incorporate joint evaluation. Patient reported measures such as Visual Analogue scale (VAS), inflammatory markers like ESR and CRP are also taken into consideration.[19]

Clinical factors that are affecting the drug response

1. Age

The probability of increasing rheumatoid arthritis rises as people age, attaining its highest rates at the age between 14 and 75 years.[20,21] Studies have shown that older people are prone to respond less efficiently to combination therapy with standard synthesis disease modifying anti rheumatic drugs[22] along with TNF inhibitors.[23-26] The evaluated individuals initiate to TNF I therapy and finally based on age the younger patients are tending good EULAR responses. Although, the impact of age on therapy outcomes is minimal.[27]

2. Gender

Several observational as well as clinical Studies have frequently shown that gender affects how patients respond to therapy. Mostly women tend to have a lower improvement to combination CSDMARDS [22] and Tissue necrosis inhibitors.[22,28-34]

3. Smoking

Research has also proved that smokers respond inadequately than nonsmokers to therapy like methotrexate, infliximab and combination therapy although this variation is not evident with rituximab. The specific reason for these inferior outcomes in smokers is not totally understood but smoking is connected to increased levels of inflammatory cytokines like TNF. TNF1 therapies are ineffective in smokers, whereas B-cell depleting therapies appear unaltered.[31,32,35-37]

4. Pathological activity

Patients with elevated levels of disorder activity often undergo worse clinical outcomes such as ongoing joint destruction detectable on radiographs.[27]

5. Body mass index [BMI]

Various mechanisms may describe about these poorer outcomes. Adipose tissue is metabolically active and the obesity helps to increase levels of pro inflammatory cytokines like TNF and Interleukin-4 along with them additional stress on weight supporting joints is also reported to be connected to these mechanisms. Raised BMI has been correlated with reduction in DMARD concentrations, due to lower absorption as well as faster drug clearance.[38,39-41]

6. Medication non-adherence

Neglecting prescribed therapies is more common than once considered, impacting about one in four individuals taking methotrexate and this can lead to poorer response to treatment. Health professionals often do not accept when individuals are non-adherent which may be affected by psychological factors.[27, 42-43]

Diagnostic tools of personalized medicine in the management of arthritis:

a. Omics

The high rate of increase in several types of omics technologies has been a result of extensive attempts to elucidate the molecular pathways underlying numerous complex human diseases. They are genomics, epigenetics, transcriptomics, proteomics and metabolomics among others. Unprecedented detail and cost-effective approaches of generating large-scale data has been made available through new methods. We discuss the present position of the omics research in rheumatoid arthritis (RA) and the manner in which it has been applied to determine markers of treatment response and also progress to the concept of personalized medicine.

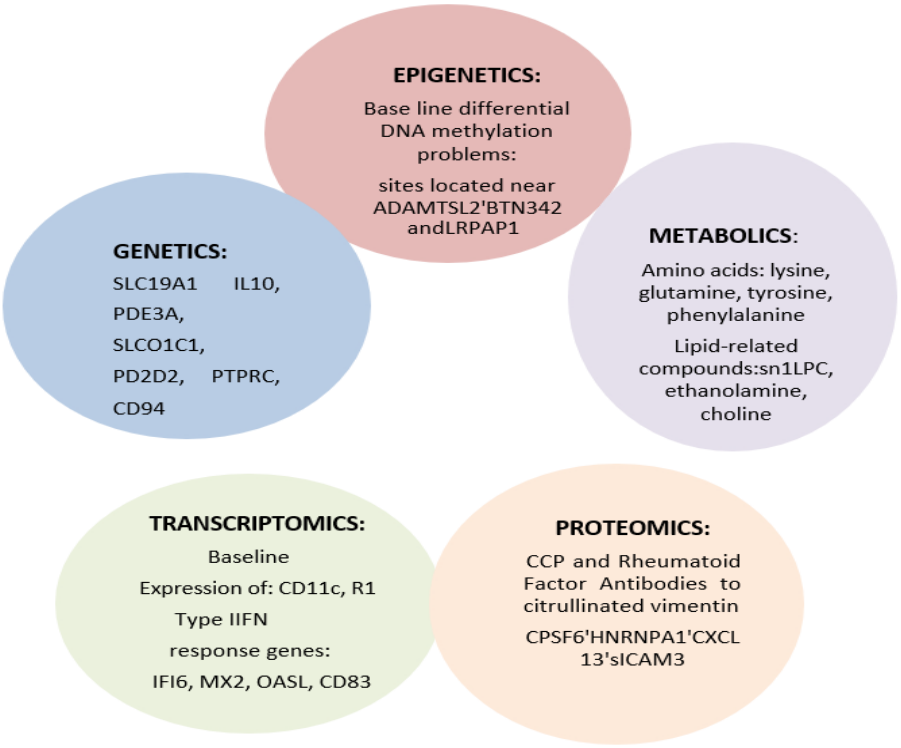

Fig. 1: Role of Personalized Medicine in Rheumatoid Arthritis.

Pharmacogenomics

Pharmacogenomics concentrates on how differences in the human genome impact drug response and with the sequencing of the human DNA in 2003 along with the drastic reduction in sequencing costs, personalized medicine has become increasingly possible. Besides TNF inhibitors, genetic variants in interleukin-6 and interleukin-6R have also been connected with therapy response, emphasizing the potential of pharmacogenomics to reveal therapeutic targets. GWAS (Genome-wide association studies) have now determined more than 30SNPs linked to TNFi Epigenetic.[44]

Epigenetics

Epigenetics is heritable and functional variation that occurs without a change in DNA sequence and can be modified by environmental exposures. The main mechanisms are the DNA methylation, histone modifications and microRNAs (miRNAs). DNA methylation is a process that clinically regulates transcription in a manner where hypo methylated regions become activated and hyper methylated ones remain silenced by the addition of methyl of CpG sites. Histone modifications include acetylation, methylation, phosphorylation and citrullination; these modify the tightness of the packaging of DNA and hence the availability of genes. MicroRNA are small non-coding RNAs which regulate gene expression post-transcriptionally. The observed histone alterations in rheumatoid arthritis are connected to the active fibroblast state, tissue destruction and relevant miRNAs such as miR-146a-5p and miR-125 b, can repress NF- B signaling and major inflammatory cytokines such as TNF-alpha and IL-6 therapy response, consisting of a strong interaction with the MAFB gene even though for many variants the exact target genes remain tentative due to complex DNA regulation. Since it is unusual that any single SNP can steadily predict therapy response, integrating various variants into polygenic risk scores may in future provide medical practitioner with practical tools to instruct personalized treatment.[45,46]

Transcriptomics

Transcriptomics genomic research where examination of gene expression profiles can be used to find associations with disease pathology and drug response in Rheumatoid Arthritis (RA). Transcriptome refers to entire RNA molecules expressed in a particular biological sample at a specific time which illustrates a highly dynamic cellular activity. Using these patterns of expression, transcriptomics can give very useful information to disease pathways and it can lead to the identification of molecular signatures that may be the cause of differences in treatment responses. Techniques that sometimes are performed in order to analyze transcriptome include: the RNA sequencing, reverse transcription polymerase chain reaction (RT- PCR) and a microarray analysis.[47,48]

Proteomics

The analysis of the entire proteins in a cell or tissue is highly complex (more so than the genome) because of variations in abundance, post-translational modifications and interactions. In Rheumatoid Arthritis (RA), disturbances in protein regulation are central to disease events and most treatments interfere with proteins directly, so proteomics presents a wide potential utility in identifying biomarkers of disease activity and treatment response.

There are two principle methods, immunoassay in which an antibody is used to identify proteins and mass spectrometry, where proteins are separated by the ratio of their mass to charge. Clinically, Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) are well- established proteomic biomarkers that assist in diagnosis and can provide important information concerning treatment variability.

In addition, further research is in progress to identify additional protein and autoantibody signatures, although this remains limited by inconsistent validation of such signatures in large cohorts. Nevertheless, the limitation to the use of proteomics in advancing personalized medicine in RA is that this approach can never be precise and individualized in the way that it should be.[49]

Metabolomics

Metabolomics is a form of omics that deals with the measurement of small molecular weight metabolites as they are the end products of genetic, transcriptomic and proteomic activity and thus indicative of the global activity of cells and tissues. Mass spectrometry, nuclear magnetic resonance are the primary technologies applicable and any of such specimens can be analyzed: blood, urine, synovial fluid, etc. In rheumatoid arthritis, metabolomics studies have been used to indicate the mechanism of the disease, severity overall as well as treatment response and extra-articular manifestations. Metabolomics has the potential of revealing biomarkers that can be used to facilitate personalized medicine by capturing any metabolic changes caused by disease processes and their therapies. There is still little inconsistency in validation of these differences in large independent studies and it remains to be seen whether these differences prove useful in clinical practice or not.[50]

Role of AI in personalized medicine in the management of Rhematoid Arthritis:

Artificial intelligence (AI) refers to the capability of robots to do activities that tend to need human intelligence. In ectopy-fast moving technological advances, AI is used in a wide range of fields, including precision medicine. ML is a subfield of AI with the ability to engage machines to identify patterns and associations in data, although without specific directions and that contrasts with the traditional technique of "hypothesis testing".

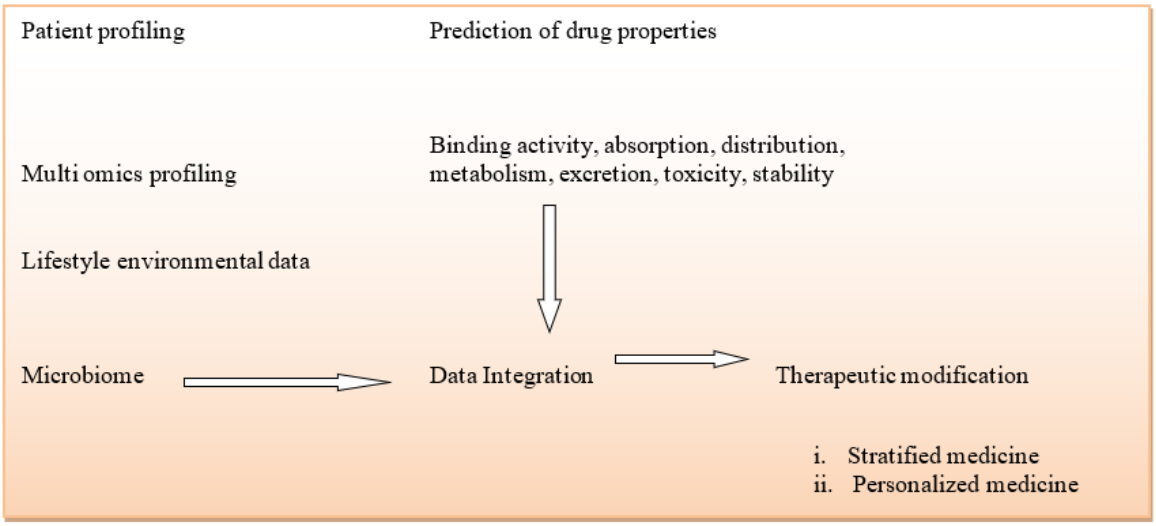

Fig. 2: Role of AI in personalized medicine.

In rheumatoid arthritis (RA), unsupervised and supervised ML have been tested. A primary research burden in this area is that large, complex data are multiplying, particularly those produced by omics technologies, in which the number of potential predictors exceeds the number of patients-a phenomenon called the curse of dimensionality. Combining this extensive amount of information to correctly forecast response to treatment is a major challenge.[51]

There is a need to integrate this clinical information with omics data including genomics, transcriptomics, proteomics and other molecular profiles to solve this problem. The increase in accuracy that comes with adding these layers of biological information has been demonstrated to be more accurate than clinical information alone. Transcriptomic data and multi-omics strategies, in particular seem to be especially practical in determining the responders and non-responders to treatment.

Although these achievements are encouraging, there are still some obstacles on the way to the implementation of ML in the clinical practice. Widely reported problems include overfitting and the fact that models perform poorly on new patients, the absence of external validation and an inconsistency in study design and inconsistency in the measurement and timing of clinical and biological endpoints. Ethical consideration also comes to play, including the black box nature of an algorithm out of which concerns are not very straightforward about treatment decision- making. However, even further integration of clinicians, biologists and data scientists is enlarging the area and ML has significant promise in the future to enhance individualized treatment plans in RA.[52]

Role of biomarkers

Cytokines are miniature proteins (520 kDa) and are involved in regulating cell communication that may activate or inhibit immune activities. They form a complex signaling network that interferes with the balance of the synovial tissue environment in promoting destructive changes in RA. Cytokines also cause increased release of inflammatory mediators and tissue-degrading enzymes by the joint cells through signal transduction. They too enhance the increase of immune cells, such as macrophages, neutrophils and dendritic cells in the joint, further aggravating inflammation and injury. Some of the main cytokines that take part in the RA are IL-1, TNF-a, IL- 6, IL-15, IL-17and IL-18 that are all central to the disease progression.

Table 1: Biomarkers in the Management of RA.

S. No.	Biomarkers	Source	Functions in RA Pathogenesis	Clinical Management
1.	TNF-α	Monocytes, macrophages, synovial fibroblast, F- cells, B-cells	Activate send othelium; induces An oblasts, IL1, IL6, IL- 8, GM-CSF; stimulates osteoclasts, inhibits osteoblasts; induces Dkk-1 bone Erosion.	Anti-TNF biologics (infliximab, etanercept, adalimumab) reduce inflammation and joint Damage[53,54]
2.	Interferon (IFN-alpha, IFN-B)	Dendritic cells, phagocytes, Fibroblasts	IFN-a: Pro inflammatory (Th1activation, autoimmunity); IFN-B: Anti- inflammatory (reducesTNF,IL-1; increases IL-10)	IFN-a signature= diagnostic biomarker; IFN-B therapy explored[55,57]
3.	Interleukin-1	Macrophages, Monocytes, fibroblast	Induces synovitis, IL pannus, cartilage and bone erosion; synergistic with TNF- α	IL-1R a therapy (anakinra) reduces inflammation[58,60]
4.	Interleukin-6	Lymphocytes, synovial, fibroblasts, osteoblast; endothelial cells	Promotes B-cells Differentiation Th17 proliferation; induces VEGF (angiogenesis); enhances Osteoclast genesis; increases CRP	IL-6 blockers (tocilizumab, sarilumab) reduce Systemic and joint inflammation[61,63]
5.	Interleukin-12/23	Dendritic cell, macrophages, antigen-presenting cells	IL-12Th1maturation, IFN- Y release; IL-23- Th17activation, IL-17, IL-6, TNF induction	Biologics targeting IL-12/23, reduce-cell autoimmunity[64]
6.	Interleukin-15	Synovium (all RA stages) T- cells, NK Cells	Induces T-cell proliferation; stimulates metalloproteinase-cartilage and bone destruction	Biomarker of RA severity; IL-15 antagonist under trials[65,66]

7.	Interleukin-17	Th17Cells, mast cells	Stimulates fibroblasts and chondrocytes MMPs; induces TNF, IL-1, IL-6; promotes angiogenesis	Elevated IL-17in serum/synovium= progression; anti-IL- 17 therapies (secukinumab)in trials[67]
8.	Interleukin-18	Dendritic cells, Macrophages, chondrocytes, fibroblasts, Osteoblasts-	Induces TNF-a, GM- CSF, IFN-γ; activates T- cells; amplifies inflammation.	High IL-18- biomarker of active disease; inhibition under investigation[68]

Phytochemicals as biomarker modulators

Plant-based secondary metabolites include phytoconstituents including alkaloids, polyphenols, flavonoids, terpenoids and glycosides which are usually induced by stress when excess reactive oxygen species (ROS) are produced. These compounds act as antioxidants by enzyme- based (such as gelatinase), non-enzyme (such as vitamin, glutathione, carotenoids, phenolic acids and tannin) antioxidants. Plant-based natural antioxidants (vitamin C, vitamin E, carotenoids and polyphenols) are useful in countering the effects of free radicals, preventing lipid peroxidation and reducing oxidative damage. Certain phytochemicals such as lycopene, 2-carotene, quercetin, apigenin luteolin, naringenin, genistein, catechins and anthocyanins have been known to regulate inflammation by inhibiting NF- 2, AP-1-and MAPK- signaling pathways to reduce the production of cytokines such as TNF-2, IL-1B, IL-6 and IL-8. Similarly, plant terpenoids and glycosides (*Stevia rebaudiana* and *Glycyrrhiza glabra*) exhibit high anti-inflammatory and immune-regulating activity. As oxidative stress and excessive release of cytokine are fundamental factors in chronic inflammatory and autoimmune diseases such as Rheumatoid arthritis, these plant-derived compounds are potentially useful as nutraceuticals or an adjunct to conventional therapy with additional advantages of fewer side effects and reduced toxicity in the long term.

Table 2: Phytochemicals as Biomarker Modulators and their role in RA.

S. No.	Phytochemicals	Source	Important bio modulators, targets	Mechanisms or roles in RA
1.	Withaferin A	*Withania somnifera*	NF-KB, AP-1, cytokines	Suppresses NF- KB. translocation; decrease pro inflammatory cytokines.[69]
2.	Triptolide	*Tripterygium wilfordii*	NF-KB, AP-1, NF-AT	Suppresses transcription factors regulating information.[71]
3.	Thymiquinone	*Nigella sativa*	TNF-α, IL-1, MAPK, NF-KB	Blocks MAPK and NF-KB; improves RA symptoms like methotrexate.[72]
4.	Geninstein	*Glycine max*	TNF-alpha, IL-1, IL-6, IL8, NF-KB	Suppresses TNF alpha induced cytokines; inhibits NF-KB activation.[73]
5.	Ginsenoside	*Panax ginseng*	Cox-2, IL-1beta, TNF alpha, IL-17	Suppresses inflammatory cytokines; protects synovial microenvironment.[74]
6.	Guggulsterone	*Commiphora mukul*	NF-KB, IKK, IL-1beta	Blocks NF-KB translocation; decrease cytokine release.[75]
7.	Hesperidin	*Rosmarinus officinalis*	Cox-2, PGE2, NO, NF-KB	Reduces cox 2,PGE2;inhibits NF-KB pathway.[76]
8.	Kirenol	*Siegesbeckia orientalis*	TNF-alphaIL-1beta, IL6, IL-17alpha	Down regulates cytokines; prevents bone erosion; increase tregs.[77]
9.	Plumbagin	*Arnebia euchroma*	IL-1, beta, Th17, pro inflammatory cytokines	Suppresses IL 1beta, Th17 response; prevents joint destruction.[78]

10.	Prim-o glucostylcimifugin	*Saposhnikora divaricata*	NF-KB, MAPK (ERK,JNK,P38)	Inhibits NF-KB and MAPK signaling, decrease cytokines.[78,80]
11.	Medecassoside	*Centella asiatica*	MMP-13, NF-KB, cytokines	Inhibits fibroblast activity; suppresses MMP-13andNF-KB.[81]
12.	Norisoboldine	*Lindera aggregate*	IL-6, PGE2, MMP-13, NF-KB	Attenuates osteoclast differentiation and bone erosion.[82]
13.	Resveratrol	*Vitis vinifera*	NF-KB, ROS, MMP.9, iNOS	Inhibits NF KB; reduces IL 1beta,TNF-alpha induced inflammation.[83]
14.	Celastrol	*Tripterygium Wilfordii*	NF-KB, MMP 9, TLR4/MyD88	Blocks NF-KB andMMP-9; inhibits inflammatory signaling.[84]
15.	Chlorogenic acid	*Hibiscus sabdariffa*	BAFF, NF-KB, MMPs	Downregulates BAFF, MMP-1/3/13; improves synovial histology.[85]
16.	Curcumin	*Curcuma longa*	NF-KB, pro inflammatory cytokines	Inhibits NF-KB; Suppresses synovial inflammation and arthritis symptoms.[86]
17.	Cryptotanshinone	*Salvia miltiorrhiza*	IL-1beta,TNF-alpha, NF- KB	Suppresses IL 1beta, IL-17: reduces joint inflammation.[87]
18.	Epigallocatechin-3- gallate	*Camellia sinensis*	FF-KB, MMP-2, chemokines	Inhibits NF-KB translocation; reduces apoptosis resistance in RA.[88]
19.	Allicin	*Allium sativum*	IL-1beta, inflammatory cytokines	Suppresses IL 1beta in chondrocytes; reduce joint swelling and inflammation. [89,90]
20.	Andrographolide	*Andrographis panculata*	NF-KB, pro inflammatory cytokines	Inhibits NF-KB Pathway decreases swelling, pain, Joint stiffness.[91]
21.	Berberine	*Berberis ariastata*	IL-17, RAFLS, COK activity	Downregulates synoviocyte proliferation; reduce bone Erosion and IL-17.[92,93]
22.	Bromelain	*Ananas comosus*	COX-2, PGE2	Inhibits COX-2, PGE2; reduces pain, swelling, cartilage destruction.[94]

CONCLUSION

The introduction of personalized medicine has become a paradigm in the understanding and treatment of rheumatoid arthritis (RA), a detachment of the traditional therapy of one-size-fits-all therapy to the personalized one. Its combination of genetic, epigenetic, transcriptomic, proteomic and metabolomic data with clinical and lifestyle variables allows prediction of the disease early, accurate diagnosis and prevention of the disease development in a targeted manner. The discovery of particular biomarkers, including TNF-alpha, IL-1, IL-6 and IL-17 has significantly enhanced the use of therapeutics in decision-making because now it is possible to select appropriate biologics and disease-modifying agents based on the molecular profile of each individual. Moreover, introduction of pharmacogenomics can streamline the effect of drugs maximizing the response and reducing the identification of adverse effects.

Predictive abilities are further empowered by the use of artificial intelligence (AI) and machine learning (ML) in the analysis of multi-omics data which further improves the personalization of the therapy. Although there are still challenges including the variability of the data, the limitations of the validation and the ethical issues, the advances in the research are still able to improve the accuracy of these technologies.

To sum up, personalized medicine in rheumatoid arthritis represents the concept of the 4P framework (Predictive, Preventive, Personalized and Participatory) with a better treatment outcome, disease burden and quality of life. With

the progressive development of science, this practice has a lot of potential in changing the way RA care is conducted into a more efficient, patient-centered and evidence-based medical practice.

Abbreviations

1. **ADAMTSL1**: A Disintegrin And Metalloproteinase with Thrombospondin Motifs-Like1
2. **APC**: Antigen Presenting Cells
3. **BAFF**: B-Cell Activating Factor
4. **BATF2**: Basic Leucine Zipper ATF -like Transcription Factor2
5. **CCP**: cyclic citrullinated peptide
6. **CD**: cluster of differentiation
7. **CLTC**: Clathrin Heavy chain
8. **COIL**: Coilin
9. **COX-2**: Cyclooxygenase-2
10. **CRP**: C-Reactive protein
11. **CXCL13**: C-X-C Motif Chemokine Ligand 13
12. **DKK-1**: Dickkopf-related Protein 1
13. **EGCG**: Epigallocatechin-3-Gallate
14. **ERK**: Extracellular Signal-Regulated Kinase
15. **GM-CSF**: Granulocyte Macrophage Colony Stimulating Factor
16. **ICAM3** : Intercellular Adhesion Molecule3
17. **IFN** : Interferon
18. **IF16**: Interferon Alpha Inducible Protein 6
19. **IKK**: IκB Kinase
20. **IL**: Interleukin
21. **IL-Ra:** Interleukin-1 Receptor Antagonist
22. **iNOS**: Inducible Nitric Oxide Synthase
23. **JNK**: c-Jun N-terminal Kinase
24. **LAMP3**: Lysosomal Associated Membrane protein3
25. **LPC:** Lysophosphsdiylcholine
26. **MAPK:** Mitogen Activated Protein Kinase
27. **MMPs**: Matrix Metallo protein kinases
28. **MX2**: MX Dynamic Like GTPase2
29. **MyD88**: Myeloid Differentiation Primary Response 88
30. **NF-AT**: Nuclear Factor of Activated Bcells
31. **NF-κB**: Nuclear Factor kappa-light-chain-enhancer of Activated B cells
32. **NK cells**: Natural killer cells
33. **NO**: Nitric oxide
34. **OASL**: 2’5’-Oligoadenylate synythase -like
35. **P38**: p38Mitogen Activated Proteinkinase
36. **PDE3A**: Phosphodiesterase 3A
37. **PGE2**:Prostaglandin E2

38. **PTPRC**: Protein Tyrosine Phosphatase Receptor Type C
39. **RA-FLS**: Rheumatoid Arthritis Fibroblast like Synoviocytes
40. **RF**: Rheumatoid factor
41. **ROS**: Reactive Oxygen Species
42. **SELENOP**: Selenoprotein P
43. **SLCO1C1**: Solute carrier organic anion transporter family member 1C1
44. **SLC19A1**: Solute carrier family 19 member1
45. **SNP**: Single Nucleotide Polymorphism
46. **Th17**: T Helper 17 cells
47. **TLR4**: Toll Like Receptor-4
48. **TNF- alpha**: Tumour Necrosis Factor Alpha
49. **Tregs**: Regulatory T cells
50. **VEGF:** Vascular Endothelial Growth Factor

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