Minireview

Indigenous Nigeria medicinal herbal remedies: A potential source for therapeutic against rheumatoid arthritis

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Impact Statement

Rheumatoid arthritis (RA) is a systemic autoimmune disorder characterized by painful joint inflammation that orchestrates destructive bone erosion. It is produced by several innate and adaptive cells of the immune systems, including macrophages, neutrophils, mast cells, monocytes, dendritic cells, B cells, and T cells. There is an avalanche of conventional drugs widely prescribed for the treatment and management of RA, but several side effects burden their therapeutic effectiveness. In Nigeria, CAM is an alternative therapeutic option for managing RA due to the preponderance of bioactive components contained in plant botanicals. We explored the bioactive compounds in the identified medicinal plants based on these folkloric claims. We probed experimental evidence to validate their anti-RA effect in different studies that employed arthritic models. Findings from the studies included in this review revealed that these bioactive compounds modulated several signaling proteins and proinflammatory cells responsible for the pathogenesis of RA.

Abstract

Rheumatoid arthritis (RA) is a debilitating disease associated with locomotion impairment, and conventional therapeutic drugs are not optimal for managing RA. There is an avalanche of medications used for the management of RA. Still, studies have shown that they are associated with severe side effects, including hepatotoxicity, retinopathy, and cardiotoxicity disorders of the central nervous system (CNS), skin, blood, and infections. Complementary and alternative medicine (CAM) is currently gaining attention as a novel panacea for managing debilitating diseases, such as RA. Nigerian folk herbal remedies are replete with a plethora of curative medicine, albeit unvalidated scientifically but with seemingly miraculous provenance. Studies of the identification of bioactive compounds present in these botanicals using advanced spectral analytical techniques have enhanced our understanding of the role of Nigerian herbal remedies in the treatment and management of RA. Interestingly, experimental studies abound that the bioactive compounds present in the extracts of plant botanicals protected animals from the development of RA in different experimental models and reduced the toxicity associated with conventional therapeutics. Validated mechanisms of RA amelioration in human and animal models include suppression of the expression of NF-κB, IL-1β, TNF-α, IL-6, IL-8, IL-17, IL-23, chemokines, TGF-β, RANKL, RANK, iNOS, arginase, COX-2, VEGFA, VEGFR, NFATC1, and TRAP in the synoviocytes. Decreased ROS, NO, MDA, carbonyl groups, and PGE_2 in the synovial fluid increased the expression of PPARα/γ; antioxidant and anti-inflammatory molecules also improve RA etiology. In this mini-review, we discuss the global burden of RA, the novel role of plant-based botanicals as potential therapeutics against signaling pathways in RA. Also addressed is the possible repurposing/reprofiling of plant botanicals to increase their therapeutic index among RA patients that patronize traditional healers in Nigeria with a global projection.

Keywords: Rheumatoid arthritis, bioactive compounds, medicinal plants, ethnomedicine, reprofiling, alternative medicine

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Introduction

RA burden is continually rising in different world regions. Globally, the incidence of RA is about 3 cases per 10,000 with a prevalence rate of 1.1%, consisting of 0.33% in South Europe, 0.50% in North European countries, and 0.11% in America, and this increases with age.[1] Between 1980 and 2019, the prevalence of RA was 460 per 100,000 population.[2] This is common among individuals between the ages of 70 years with an age-stratified majority of 1.63%,[3] with women having a higher risk of developing RA (about twice more likely) than men. Although the high odd ratio is not

precise, previous studies identified genetic factors and hormones[4] as predisposing risk factors for RA. These identified factors can induce anti-RA drug resistance, as seen with methotrexate, naproxen, dexamethasone, and other anti-RA drugs.[5–8] Experimental and clinical studies show that the dysregulation of sex hormones influences immune reactivity in RA patients. These hormonal and immunological perturbations contribute to the influx of more lymphocytes and monocytes in the synovial fluids of female individuals than in their male counterparts and higher antigen-presenting activity and mitogenic responses. An imbalance in sex hormones, characterized by lower immunosuppressive androgen and higher immunostimulatory estrogens, may reduce the efficacy of anti-RA therapies.[5,6,9]

There is a lack of data in Africa on the prevalence of RA.[10–12] Data extracted from a systematic analysis of 9 (out of 10 included) studies in sub-Saharan Africa and published from 1968 to 1988 estimated a crude prevalence of 0.36% for RA.[11] A systematic review and meta-analysis of population-based studies from 11 African countries – urban and rural settings – estimated different crude prevalence. In urban/semi-urban setting, the estimated crude prevalence was 0.13% (Algeria),[13] 0.6% (Democratic Republic of Congo),[14] 2.5% (South Africa),[15] and 0.12% (Nigeria)[16], while in the rural location, the estimated crude prevalence was 0.0% (Nigeria),[17] 0.07% (South Africa),[15,18,19] 0.29% (Egypt),[20] and 0.28% (Lesotho)[21] in patients between 15 and 18 years and above. In adults above 65 years of age living in rural areas, RA prevalence per country ranged from 0.40% in Nigeria[17] to 29.5%,[22] 29.7%,[23] and a maximum of 82.7%[24] in South Africa. The disparity in the prevalence of RA in developing and developed countries may stem from the widespread use of complementary and alternative medical approaches[25–27] in different continents of the world. While this may be true in a rural setting, a survey to estimate the proportion of hypertensive patients seeking various health care system in an urban center in Nigeria revealed that 63.4% of the respondents relied solely on the hospitals, 5% sought only treatment from chemists or patent medicine vendor, 7.0% depended on the hospital, chemist – a pharmacy –, and traditional medical care, 6.4% treat and manage their ailment from hospital and chemistry medical care, and 1.4% relied on medical care from the chemist and traditional herbal medical setting. Interestingly, no respondents relied solely on CAM.[28] This disparity may be due to the low premium placed on the Nigerian traditional practice in recent times, the ineffective licensing body for controlling CAM practice in Nigeria, and the lack of evidence-based research to properly elucidate the ethnomedicinal benefits of plant resources in Nigeria. Here, we discuss the various medicinal plants and herbs as a novel therapeutic target for the treatment and management of RA in Nigeria and delineate the mode of action of the most active bioactive in these plants against intracellular signaling pathways that drive RA.

Pathophysiology of RA

RA is a systemic autoimmune disorder characterized by painful joint inflammation that orchestrates destructive bone erosion. Symptoms include pain and stiffness, swollen joints, fluid retentions in the ankles, fatigue, mouth dryness, nodules on the skin, joint redness, and depression if prolonged.[29–31] A common feature of RA is the loss of synovial homeostasis, which is characterized by persistent articular tenderness and joint inflammation orchestrated by the proliferating tissues of the synovial fibrocytes[32] and trafficking of the cells of the innate and adaptive immune systems, including T and B lymphocytes, natural killer (NK) cells, dendritic cells, neutrophils, and macrophages into the inflamed synovium;[33,34] hypertrophy of the synovium which leads to the formation of pannus that invades and destroys local articular networks[35] and the expression of proinflammatory cytokines, chemokines, and metalloproteinases by the cells of the pannus resulting in the progressive destruction of the joints of RA patients.[36] Early disease diagnosis is an essential strategy to reduce the burden of RA. Autoantibodies are the most attractive markers for detecting RA in patients.[37] Two features, including rheumatoid factor (RF) and anticitrullinated protein/peptide antibodies (ACPA), have been included in the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA.[38] RF is a classical autoantibody present in 70–80% of patients with RA but is burdened with reduced specificity.[39] Unlike RF, ACPA is a more specific marker for RA and usually co-exist with RF.[40] ACPA is present in 50% of patients with RA[41] and can autonomously promote bone remodeling by inducing differentiation of bone-resorbing osteoclasts.[42] Assays for detecting ACPA have been described to have excellent diagnostic and predictive markers for RA and may aid in the early detection of patients who need timely and uncompromising treatment. The identification of ACPA in the pathology of RA allows the classification of RA into two different disease subsets: ACPA-positive and ACPA-negative RA. These two disease subsets have a similar clinical presentation[43] but differ in the disease course and response to treatment.[43–46] ACPA-negative RA is mild, and patients with this disease are more likely to achieve drug-free remission.[47] Unlike ACPA-negative RA, ACPA-positive RA associated with a worse prognosis characterized by the higher rates of erosive damage[43] has different risk factors with most genetic associations[48–50] and environmental risks, such as smoking[51,52] and alcohol abstinence.[53,54]

The exact etiology of RA is unclear; however, several genetic factors (major histocompatibility complex [MHC] Class II DR4 haplotype and protein tyrosine phosphatase non-receptor type-22 [PTPN22] genes) and environmental factors (viruses, bacteria, tobacco smoke, and silica mineral) that contribute to an increased risk of the disease have been identified.[55] Genetically, the human leukocyte antigen (HLA) is strongly associated with RA.[56] Based on twin studies, the heritability of RA was estimated to be about 60%, while HLA contributed 11–37% to the overall heritable trait.[57,58] Shared epitopes (SE) alleles, such as HLA-DRB1*01 and DRB1*04 code, a five amino acid sequence motifs in residues 70–74 of the HLA-DRβ chain, have been implicated in the pathogenesis of RA.[59,60] Other non-SE HLA-DRB1 alleles, including HLA-DRB1*03, DRB1*13, and DRB1*15, have also been associated with RA susceptibility.[58,61] Based on this evidence, it has been demonstrated that individuals with a high copy number of SE are susceptible to RA, and this may

vary across different ethnic nationalities. In a comparative study to investigate whether ethnic differences exist in the effect of the shared epitope and selected cytokine gene polymorphisms on the susceptibility and severity of RA in 678 patients and 591 healthy patients randomly selected across Syria (Damascus) and France (Rhône-Alpes area), it was observed that the SE and tumor necrosis factor-alpha (TNF-α) polymorphism were significant in the Syrian population than in France population, with an odds ratio (OR) of almost 10 for the homozygotes.[62] Extensive genome-wide association studies (GWAS) have identified over 100 loci involved in the pathogenesis of RA.[63,64] The second strongest association with RA is the PTPN22 which encodes lymphocyte tyrosine phosphatase (Lyp), a negative regulator of T cell receptor signaling. Single-nucleotide polymorphism (SNP) of the non-HLA gene is also associated with the pathogenesis of RA.[58] These genes are known to regulate immune function, and they include cytotoxic lymphocytes associated with protein 4 (CTLA4) and signal transducer and activator of transcription 4 (STAT4), tumor necrosis factor receptor-associated factor (TRAF1), chemokine receptor CCR6, interferon regulator factor (IRF5), and peptidyl arginine deiminase 14 (PAD14). STAT4, CTLA4, and PTPN22 work in tandem to promote T cell stimulation, activation, and differentiation into effector T cells, while other genes, including TRAF1 and IRF5, drive nuclear factor-kB (NF-κB)-dependent signaling. Progress has been recorded in determining the relative contributions and the interaction of these genes in conferring the risk of ACPA-positive and ACPA-negative RA (reviewed in Holoshitz[65] and Edilova *et al.*[66]).

Unlike genetic findings, environmental factors, including smoking, alcohol, vitamin D, protein and red meat, oral contraceptives, birth weights, breastfeeding, socioeconomic status, and geographical locations (reviewed in Liao *et al.*[67]) and infectious agents, such as Epstein–Barr virus, *Aggregatibacter actinomycetemcomitans*, and *Porphyromonas gingivalis* (reviewed in Sakkas *et al.*[68]), play a significant role in the pathogenesis of RA. These risk factors trigger RA by influencing the expression of ACPA seropositive RA in HLA-DRB1 patients.[69] It is noteworthy to state that these risks factors are not directly involved in the pathophysiology of RA. Still, they reinstruct the immune system to produce chemicals that recognize and react with self-antigens, leading to the manifestation of RA (Figure 1). The innate and adaptive immune cells, MHC-II protein, co-stimulatory signals, and soluble mediators are heavily implicated in the pathogenesis of RA.[66,70,71] A dysregulation in the immune system cells following exposure to these predisposing factors has been involved in autoimmune disorders and RA.[72–74]

Intracellular signaling as therapeutic targets of RA

In addition to the factors that drive RA, intracellular signaling pathways have been recognized as significant hot spots for the development of RA during chronic inflammation. There is an exciting link between signaling networks and immune system priming. This communication is often driven by soluble factors, including cytokines, growth factors, and dangerous signals, either autocrine or paracrine. The release of these cues is stringently regulated to maintain homeostatic balance, characterized by a balance in proinflammatory and anti-inflammatory ratios. However, exposure to infectious agents can breach this "biological trust," tipping the balance favoring proinflammatory cues. It has been shown that the elevation of proinflammatory cytokines in the synovium of a healthy joint can dysregulate synovial intracellular signaling networks known to regulate the immune cells, synoviocyte survival, and cartilage apoptosis in RA patients.[75–77] Several scientific claims attribute the dysregulation of several intracellular networks to the development of RA. In the current review, we reviewed the roles of JAK/STAT, SAPK/MAPK, PI3K/AKT/mTOR, spleen tyrosine kinase (Syk), SphK/SIP, TBK1, RIPK1, Bone marrow tyrosine kinase gene in chromosome X (Bmx), and NIK in the pathogenesis of RA.[78]

The Janus kinases (JAK) play an important role in the initial step of cytokine-mediated signaling. It is activated by several arrays of cytokines and growth factors, including IL-2, -3, -4, -5, -6, -9, -10, -11, -12, -13, -15, GM-CSF, IFN-α, -β, -γ, leptin, erythropoietin, and thrombopoietin.[79–82] The binding of these soluble mediators with cognate receptor automatically induces a ligand-mediated receptor dimerization/oligomerization, transphosphorylation, and activation of JAK, which then phosphorylates signal transducers and activators of transcription (STAT). pSTAT dissociates from the complex, dimerizes, and egresses into the nucleus, where it orchestrates the transcription of several genes, especially matrix metalloproteinase (MMP). Due to the redundancy of JAK, following activation, it can drive the activation of mammalian target of rapamycin (mTOR), which is necessary for the survival of the synoviocytes, through upstream rousing of the PI3K/Akt signaling (Figure 2). The increased expression of MMP-1, -2, -9, and -13 in the synoviocytes triggers the degradation of articular cartilage extracellular matrix proteins, such as aggrecan via proteolytic cleavage between $Glu^{374–374}Ala$, $Ser^{341–342}Phe$, and $Glu^{2047–2048}Ala$ bonds.[83] In addition, MMP-9 can drive the activation and expansion of neutrophils and monocyte–macrophages and release proinflammatory cytokines in the synoviocytes, thus distorting the physiological balance between proinflammatory and anti-inflammatory mediators.[84–86] These pieces of evidence imply a positive feedback loop between cytokines and MMPs.

Phosphatidylinositol 3-kinase (PI3K)/serine-threonine receptor or protein kinase B (Akt)/mTOR signaling cascade has significantly been implicated in cancer and RA.[87–89] PI3K, a major effector downstream of receptor tyrosine kinases (RKTs) and G protein-coupled receptors (CPCRs), is activated in response to cytokines, growth factors, and hormones, leading to PI3K-mediated conversion of phosphatidylinositol-4,5-bisphosphate (PIP_2) to phosphatidylinositol-3,4,5-trisphosphate (PIP_3). PIP_3 then mediates the recruitment of inactive Akt from the cytosol to the plasma membrane, where Akt undergoes dual phosphorylation at Thre308 and Ser473 and becomes active. At this state, Akt can now phosphorylate mTOR and a host of other target proteins that regulate cell proliferation (Figure 2). Activation of PI3K/Akt/mTOR signaling cascade is implicated in RA pathogenesis through the proliferation of fibroblast-like cells, increased production of $CD4^+$ T cells, neutrophil, macrophage, and eosinophil

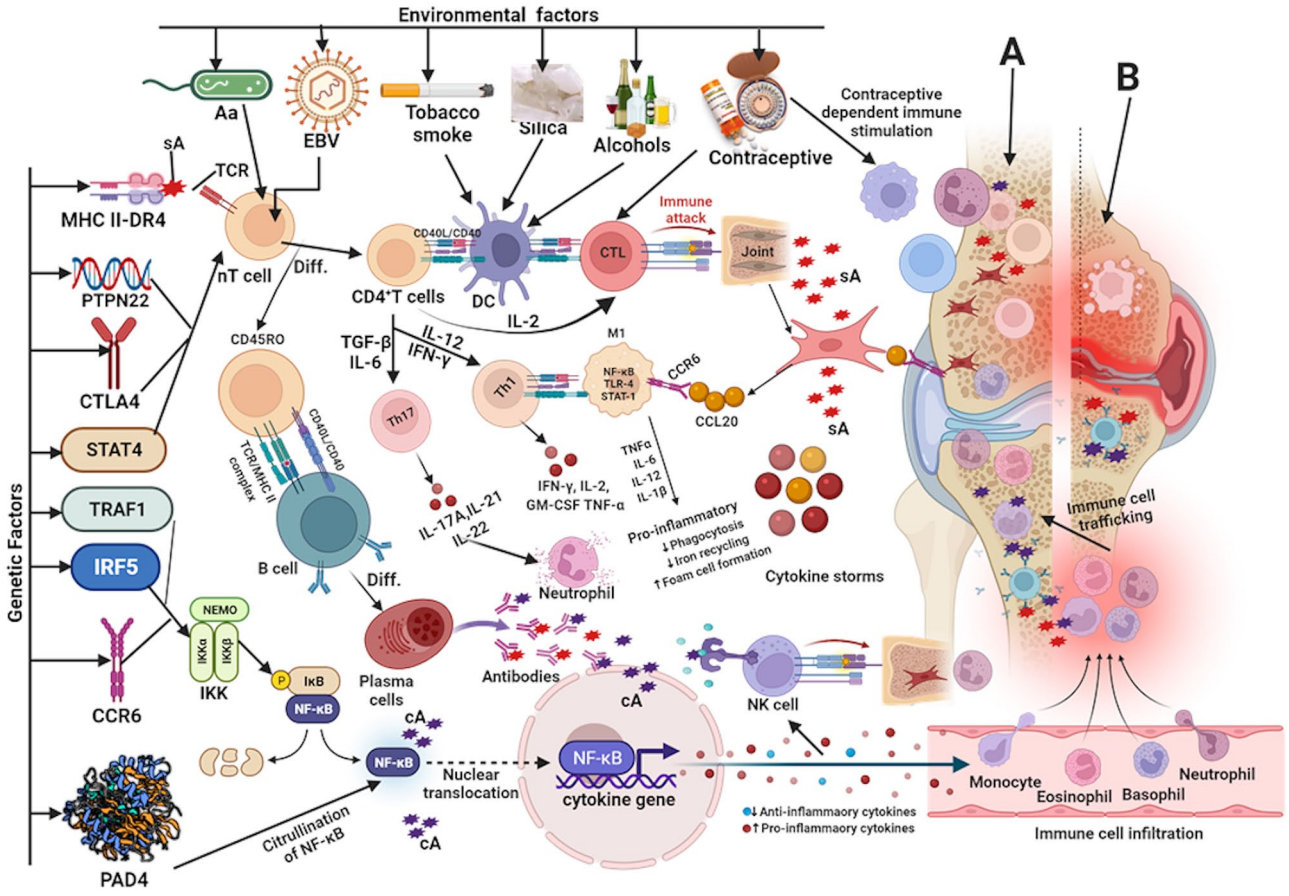

Figure 1. Genetic and environmental factors that drive RA. Several genetic and environmental factors orchestrate the pathology of RA. Dysregulation of genes, such as MHC-II DR4, PTPN22, CTLA4, and STAT4, can trigger autoantigens' uncontrolled processing and presentation to naïve $CD4^+$ T cells. The MHC-II/peptide complex's binding with TCR induces the necessary signals needed to drive naïve $CD4^+$ T cell activation, proliferation, and differentiation into effector cells. Depending on the cytokine signatures, effector $CD4^+$ T cells can polarize into proinflammatory T cell lineages, including Th1 cells (in the presence of IL-12 and IFN-γ) and T_h17 cells (in the presence of TGF-β and IL-6). These cells release proinflammatory cytokines, such as TNF-α, IFN-γ, IL-2, GM-CSF, IL-17A, IL-21, and IL-22. While cytokines released by Th1 cells drive the activation macrophages, those released by T_h17 cells orchestrate the activation and degranulation of neutrophils. $CD4^+$ T cells can use either license DCs through CD40L/CD40 interaction and produce IL-2 needed for the activation and proliferation of CD8T cells into effector CD8T cells expressing perforins, granzymes, and other program cells mediators. These bioactive factors are known to orchestrate an immune attack on healthy joints or mediate B cells' activation, proliferation, and differentiation into plasma cells and secretory antibodies through the CD40L/CD40 interaction. The resulting antibodies bind to autoantigens and other citrullinated antigens to form immune complexes and attack healthy joints. TRAF1, IRF5, and CCR6 also drive RA pathogenesis. Dysregulation in these gene expressions may switch on IKK, leading to the degradation of IκB and NF-<UNK>B's exit of NF-κB into the nucleus. It mediates the transcription of several cytokine genes and releases several proinflammatory cytokine mediators. The imbalance in proinflammatory and anti-inflammatory cytokines (cytokine storms) will trigger the infiltration and trafficking of proinflammatory cells into the synoviocytes and the activation of NK cells to attack healthy joints. The interaction of proinflammatory cells through their PRRs (e.g. TLRs) with danger signals released by dead synoviocytes and PAD4-induced citrullinated autoantigens will further increase the inflammatory burden of the synovial microenvironment, enhance cytokine storms and foam cell formation. Altered expression of CCR6 on the innate and adaptive cells and their interaction with CCL20 on synoviocytes results in the recruitment of immune-competent cells into the synovial microenvironment. Environmental factors, such as *Aa* EBV, tobacco smoke, silica, alcohols, and contraceptives, also reinstruct the immune system favoring immunocompetency, thus exposing healthy joints (A) to more proinflammatory cues, chronic inflammation, and destructive bone erosion. They are further characterized by swollen joints, joint redness, hypertrophy of the synovium, and formation of pannus, leading to joint destruction and derangement of the synovium (B). (A color version of this figure is available in the online journal.)
The scheme was modeled with Bioredender.com by Arunsi U.O.
MHC-II: Major histocompatibility complex; PTPN22: Protein tyrosine phosphatase non-receptor type-22; CCTL4: Cytotoxic T-lymphocyte antigen 4; STAT4: Signal transducer and activator of transcription 4; CD: Cluster of differentiation; TCR: T cell receptor; IL: Interleukin; IFN: Interferon; TGF-β: Transforming growth factor-beta; TNF-α: Tumor necrosis factor-alpha; GM-CSF: Granulocyte-macrophage colony-stimulating factor; Th1: Type 1 T helper; T_h17: T helper 17 cells; DC: Dendritic cells; TRAF1: TNF receptor-associated factor 1; IRF5: Interferon regulatory receptor 5; CCR6: Chemokine receptor 6; IKK: Inhibitor of kappa B kinase; IκB: Inhibitor of NF-κB; NF-κB: Nuclear factor-kappa-light-chain-enhancer of activated B cells; NK: Natural killer cells; TLR: Toll-like receptor; PAD4: Protein arginine deiminase 4; CCL20: Chemokine (c-c motif) ligand 20.

chemotaxis, mast cell degranulation, activation, maturation and survival of immunocompetent T and B cells synovial osteoclast formation, bone erosion, and cartilage loss.[87,90–93]

Stress-activated protein kinase/mitogen-activated protein kinase (SAPK/MAPK) are essential signaling nodes that drive RA pathogenesis.[94] In mammalian cells, there exist four distinct groups of SAPK/MAPK, including extracellular signal-related kinases (ERK)-1/2, c-Jun-N-terminal kinase (JNK)-1/2/3, p38 proteins (p38α/β/γ/δ), and ERK5. In the presence of proinflammatory stimuli such as lipopolysaccharide (LPS), TNF-α, and Il-1.[95,96] These proteins are activated by specific mitogen-activated protein kinase kinases (MAPKKs): MEK1/2 activates ERK1/2, MKK 3/6 activates p38, MKK 4/7 activates JNKs, and MEK 5 activates ERK 4 (Figure 2). Activation of SAPK/MAPK is known to drive the activation of NF-κB and transcription of proinflammatory

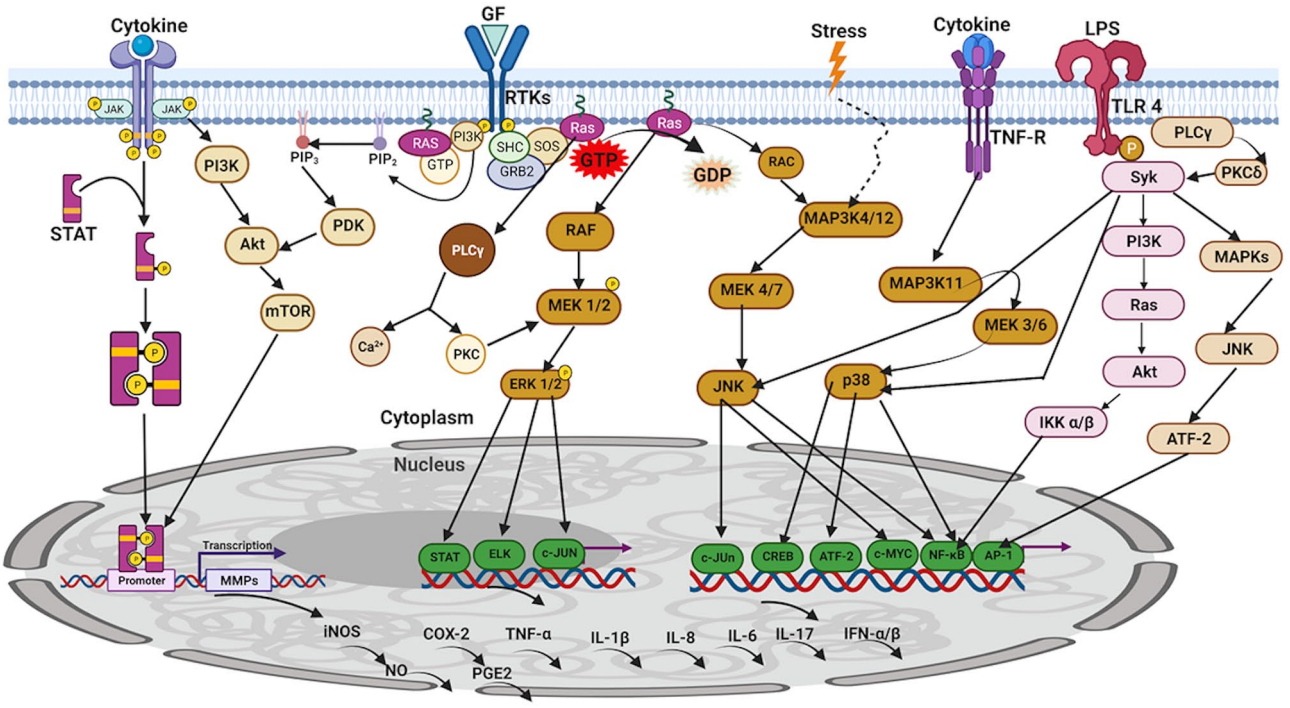

Figure 2. RA pathogenesis through the JAK/STAT, PI3K/Akt/mTOR, SAPK/MAPK, and Syk signaling networks. Several factors, such as cytokines, growth factors, stress, and danger signals, can orchestrate the stimulation of intracellular signaling networks. The binding of cytokines to the extracellular domain of the JAK receptor induces a conformational change in the cytoplasmic domain of the receptor with simultaneous phosphorylation of JAK. Activating JAK then phosphorylates STAT, leading to STAT dimerization and translocation into the nucleus to orchestrate the transcription of MMPs and the release of several soluble factors involved in the pathogenesis of RA. In addition, JAK can drive the activation of mTOR through the upstream induction of the PI3K/Akt signaling nodes. PI3K, a major effector downstream RTKs and GPCRs, is activated following the binding of growth factors to their cognate receptors. On activation, P13K mediates the transformation of PIP2 into PIP3, which then phosphorylates Akt directly or indirectly through PDK. Active Akt phosphorylates mTOR, a downstream effector node necessary for the synoviocytes' growth, proliferation, and survival. Through the stimulation of SHC adapter protein and the recruitment of other proteins, such as Grb2 and SOS (a GEF that facilitates the exchange of GDP to GTP), Ras is roused to direct signaling through the Raf/MEK1/2/ERK1/2 axis. Phosphorylated ERK exits into the nucleus and mediates the transcription of genes under the control of STAT, ELK, and C-jun. Ras can also activate RAC, which mediate the activation of the SAPK/MAPK pathway. SAPK/MAPK is activated following stress. Precisely, MAP3K4/12 activates MEK4/7, which in turn activates JNK. JNK then phosphorylates and regulates the activities of transcription factors, including c-JUN, C-MYC, and NF-κB. In addition, cytokine binds to TNF receptor and orchestrates a conformational change in the cytoplasmic region of the receptors and activates MAP3K11, which activates MEK3/6. MEK3/6 then activates p38, which then phosphorylates and regulates the activities of transcription factors, including CREB, ATF-2, and NF-κB. Also, a dangerous signal, such as LPS, binds to TLR4 and phosphorylates syk. pSyk phosphorylates and activates JNK, which regulates other transcription factors' activities. In addition, pSyk can activate IKKα/β downstream along PI3K/Ras/Akt axis. On activation, IKKα/β enhances the nuclear translocation of NF-κB by phosphorylating and marking IκB for proteasomal degradation. The activity of Syk is further reinforced by PKCδ, an effector that PLCγ activates following LPS/TLR4. Due to the redundant nature of signaling proteins, Syk can also activate MAPKs, which activates JNK. JNK, in turn, activates ATF-2. On activation, ATF-2 activates AP-1 to regulate the expression of several genes involved in RA pathogenesis. The aftermaths of the altered JAK/STAT, PI3K/Akt/mTOR, SAPK/MAPK, and Syk signaling networks are an upsurge in the expression rate of genes encoding soluble factors, including iNOS, NO, COX-2, PGE2, TNF-α, IL-1β, IL-8, IL-6, IL-17, and IFN-α/β. (A color version of this figure is available in the online journal.)
The scheme was modeled with Bioredender.com by Arunsi U.O.
IKK: Inhibitor of kappa B kinase; IκB: Inhibitor of NF-κB; NF-κB: Nuclear factor-kappa-light-chain-enhancer of activated B cells; LPS: Lipopolysaccharide; TLR: Toll-like receptor; STAT: STAT4: Signal transducer and activator of transcription 4; JAK: Janus kinase; GF: Growth factor; RTKs: Receptor tyrosine kinases; TNF-R: Tumor necrosis factor receptor; PI3K: Phosphadylinositol 3-kinase; PDK: Phosphoinositide-dependent kinase; Akt: serine threonine receptor or protein kinase B; mTOR: mammalian target of rapamycin; PIP_2: Phosphatidylinositol-4;5-bisphosphate: PIP_3: Phosphatidylinositol-3;4;5-trisphosphate; SAPK/MAPK: Stress-activated protein kinase/mitogen-activated protein kinase; ERK: Extracellular signal related kinases (ERK)-1/2; JNK: c-Jun-N-terminal kinase; p38α/β/γ/δ: p38 proteins; MAPKKs: Mitogen-activated protein kinase kinases; MEK: MAPK/ERK kinases; MMP: Matrix metalloproteinase; GDP: Guanosine nucleotide diphosphate; GTP: Guanosine nucleotide triphosphate; Grb2: Growth receptor bound protein 2; SOS: Sons of Sevenless; PLCγ: Phospholipase C-gamma; PKC: Protein kinase C; Syk: Spleen tyrosine kinase; ATF-2: Activating transcription factor -2; ELK: ETS Transcription factor ELK 1; AP-1: Activator protein 1.

mediators, including MMPs, TNF-α, IL-1, and IL-6 in the synovial tissues.[97,98] Furthermore, an increase in these mediators' expression can orchestrate the infiltration and trafficking of proinflammatory cells into the inflamed joints and cause joint destruction.[99]

Syk is a non-RKT and consist of two members, Syk and ZAP70.[100] While Syk is widely expressed in all hematopoietic lineage cells, ZAP70 is restricted to NK cells and T cells.[101] In response to proinflammatory cytokines, pathogens, danger signals, growth factors, and physical stress trigger the activation of Syk.[102] The danger signal (LPS) binding with TLR4 results in the phospholipase C (PLC)-dependent PKCδ, MAPKs, and IKK activation. Specifically, active PKCδ mediates the phosphorylation and activation of Syk. On activation, Syk amplifies the JNK, p38, and ERK signaling nodes with a concomitant upregulation of c-Jun, c-Fos, ATF-2, and AP-1 (Figure 2). These transcription factors drive the transcription of the COX-2 gene. In addition, the activation of IKKα/β along the Syk/PI3K/Ras/Akt/ axis triggers the activation of the NF-κB pathway and subsequently induces the expression of iNOS.[103] The expression of COX-2 and iNOS in synovial tissues has been implicated in the pathogenesis of RA. Crofford[104] observed that increased expression of COX-2 is associated with altered expression of MPPs, increased resistance to apoptosis, and generation of angiogenic factors. In another study, Scott[105] demonstrated that the

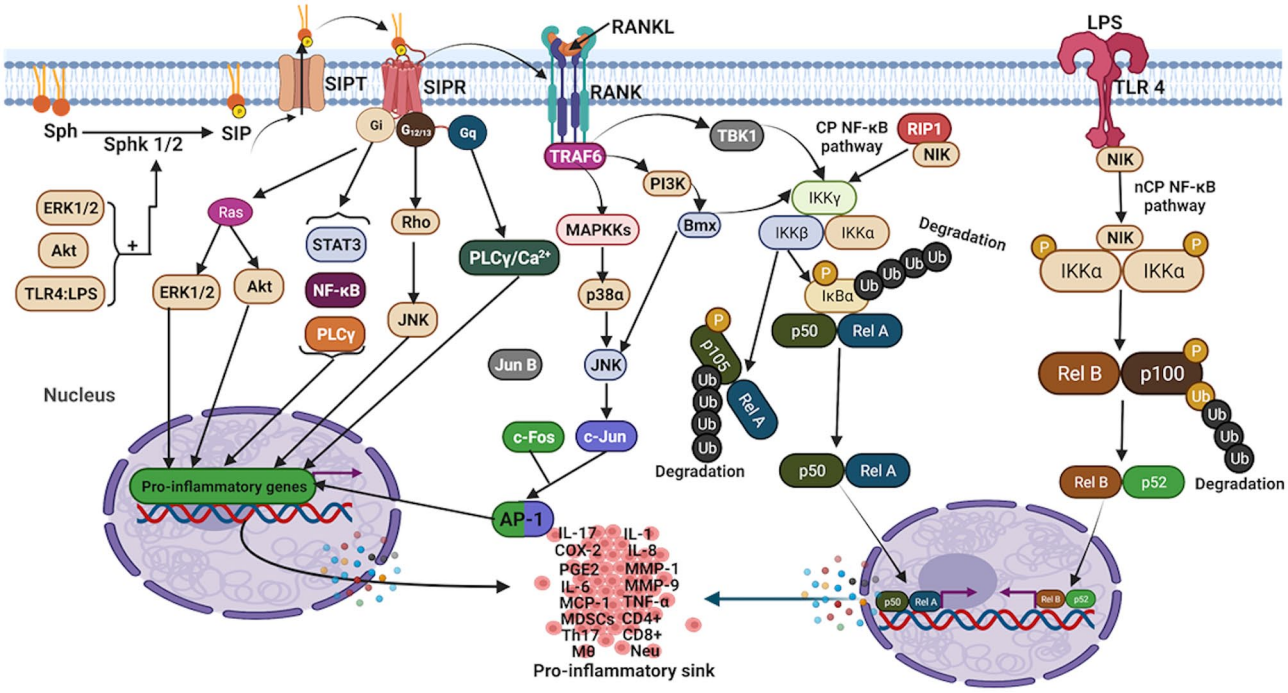

Figure 3. RA pathogenesis through the Sphk/SIP, Bmx, TBK1, RIPK1, and NIK signaling. Signaling through Sphk/SIP, Bmx, TBK1, RIPK1, and NIK has been observed to facilitate the development of RA. ERK1/2, Akt, and high LPS/TLR4 binding activate the activity of Sphk. SphK then mediates the conversion of Sph to SIP, thereby increasing the intracellular level of SIP. An upsurge in SIP level leads to the egression of SIP through the SIP transporter to the plasma membrane, where it binds to SIP receptors and induces a conformational change in the cytoplasmic site of the receptor. Concurrent induction of several signaling nodes coupled to G protein, including G_i, G_q, $G_{12/13}$ and Rho. On activation, G_i activates Ras, which in turn phosphorylates and activates ERK1/2 and Ras and phosphorylates and activates STAT3, NF-κB, and PLCγ. Furthermore, G_q activates PLCγ/Ca^{2+} while $G_{12/13}$ activates rho, which activates JNK. The interaction of SIP and its cognate receptor could trigger signaling through the RANK/RANKL pathway, leading to the activation of TRAF6. The effect of TRAF6 is multidimensional, and it can activate MAPKKs, PI3K, or TBK1 to switch on AP-1 and NF-κB pathways downstream. In the TRAF-mediated AP-1 signaling, TRAF6 conditions MAPKKs to activate p38α, activating JNK. JNK then activate c-JUN, and the dimerization of c-JUN with c-FOS forms AP-1. The length of activation of AP-1 can be reduced through TRAF/PI3K signaling, which acts as Bmx and conditions it to activate JNK. These signaling molecules act on several gene-encoding soluble factors that alter the normal synovial microenvironment. The activation of NF-κB is triggered by the activation of TBK directly by TRAF6 or indirectly through the TRAF6/PI3K axial stimulation of Bmx. TBK1 and Bmx trigger the CP of NF-κB by acting on the IKK complex. TBK1, RIPK1, and NIK rouse the activity of IKK. In the CP pathway, IKKβ phosphorylates and tags IκB and p105 for proteasomal degradation, thereby releasing RelA/p50 to egress into the nucleus, enhancing the transcription of several genes that encode proinflammatory soluble mediators. In the nCP, NIK solely activates IKKα, one of the catalytic subunits of the IKK complex. Activate IKKα, then phosphorylate and tag p100 for proteasomal processing, and free RelB from the inhibitory complex. The degradation of p100 automatically promotes the expression of p52, which interacts with RelB and exits the cytoplasm into the nucleus, where they mediate the transcription of gene-encoding soluble factors and inflammatory cells known to drive RA, including Cox-2, PGE_2, TNF-α, IL-17, IL-8, IL-6, MCP-1, MMP-1, MMP-9, MΘ, Neu, Th17 cells, CD +, and $CD8^+$ cells. (A color version of this figure is available in the online journal.)
The scheme was modeled with Bioredender.com by Arunsi U.O.
Sph: Sphingosine; Sphk: Sphingosine kinase; SIP: Sphingosine-1-phosphate; SIPR: SIP receptor; SIPT: SIP transporter; Cox-2: Cyclooxygenase-2; MΘ: Macrophages; Neu: Neutrophils; Bmx: Bone marrow tyrosine kinase gene in chromosome X; RIPK1: Receptor interacting protein kinase-1; TBK1: Transforming growth factor-beta-activated kinase-1; NIK-2: NF-κB-inducing kinase-2; CP: Canonical pathway; nCP: non-canonical pathway.

expression of Syk in the synovial tissues of propane-induced arthritis correlated with arthritic severity and joint damage. Syk dysregulation is associated with altered immune functions in the synovial tissues of arthritic patients because it can drive activation, expansion, and differentiation of T cells, phagocytosis of macrophages, and oxidative burst by neutrophils. Also involved in the infiltration and trafficking of immunocompetent cells into the inflamed joints-as seen in RA.[106,107]

Sphingolipids are the most bioactive class of lipids involved in the organization of cellular structure, metabolism, and regulation.[108] The intracellular level of sphingolipid derivative sphingosine-1-phosphate (SIP) has been correlated to several inflammatory disorders, including RA.[109] Sphingolipid is converted to SIP by sphingosine kinase (Sphk 1/2).[110] Studies have shown that increase in the expression of ERK1/2, Akt, and TLR4 enhances the activity of Sphk1/2 and promotes the intracellular level of SIPs.[111,112] Some enzymes, including SIP lyase[113] and lipid phosphate diphosphatase (LPP),[114] have been observed to degrade SIPs as a salvage mechanism to depress signaling along the Sphk/SIP/SIPR axis. Where the activities of these enzymes are not amplified following chronic inflammation, the level of SIPs accumulates intracellular such that they can permeate through the SIP transporter into the extracellular space of the plasma membrane and bind to SIP receptors (SIPR1-5). This binding triggers a conformational change in the receptor's cytoplasmic region, orchestrating the activation of multiple signaling pathways through coupling to G proteins-G_i, G_q, $G_{12/13}$ and Rho and subsequently activating various downstream signaling nodes, including Ras, ERK1/2, Akt, JNK, STAT3, NF-κB, PI3K, PLCγ, Ca^{2+}, and PKC[115,116] (Figure 3). Sphk-mediated SIP/SIPR interaction could activate RANK/RANKL signaling known to commit the joint to chronic inflammation, destruction of cartilage, and bones during the pathogenesis of RA.[117,118] The induction of RANK/RANKL signaling results in the stimulation of TRAF6, which in turn orchestrates the activation of MAPKKs, PI3K, and TBK1

to mediate the activation of several transcription factors, including AP-1 and NF-κB downstream. Dysregulation in signaling along the SIP/Sphk axis, mainly during infectious diseases, has been greatly attributed to the development of RA. Emerging evidence revealed that the activity of Sphk and the expression of SIP promote the recruitment of proinflammatory immune cells (MDSCs, Th17 cells, $CD3^+$, $CD4^+$, and $CD8^+$ T cells),[114,119] synthesis of proinflammatory mediators, such as IL-8, MCP-1, MMP-2, MMP-9,[120] expression of cyclooxygenase-2 (COX-2), and release of prostaglandin E_2 (PGE_2), thereby increasing synovial inflammation and osteoclast number.[119]

Bmx is a member of tyrosine kinase expressed mainly in granulocytic and monocytic lineages of the hematopoietic cells,[121,122] and also in the endocardium of the heart and endothelium of the arteries.[123] During inflammation, signaling through Bmx is mediated by IL-3 and G-CSF in the presence of PI3K. It is necessary for the differentiation of myeloid progenitor cells,[124] generation IL-8, and activation of p38 MAPK, JNK, and NF-κB.[125] In the arthritic model, activation of Bmx was found to be associated with paw swelling, infiltration of inflammatory cells into the tarsal and metatarsal axes, hyperplastic synovium cartilage damage, and bone erosion.[125]

The activities of receptor-interacting protein kinase-1 (RIPK1), transforming growth factor beta-activated kinase-1 (TBK1), and NF-κB-inducing kinase-2 (NIK-2) have been recognized to drive the development and progression of RA.[126–128] The expression of these proteins is integral in the activation of the Nuclear factor-kappa-light-chain-enhancer of activated B cells (NF-κB). NF-κB is an important transcription factor that regulates cellular processes, including cell growth and survival, immune surveillance, and inflammation.[129,130] It consists of five family members, including RelA (p65), RelB, c-Rel, NF-κB1 (p105/p50), and NF-κB2 (p100/p52). The activation of NF-κB occurs either through the canonical pathway (CP) or non-canonical pathway (nCP) and is orchestrated by inflammation,[131] pathogens,[130] or stress.[132] At the same time, the activation of the CP is orchestrated by the interaction of inflammatory cytokines, such as TNF-α, danger-associated molecular patterns (DAMPs), or pattern-associated molecular patterns (PAMPS). Specific receptors – TNF-R, TLRs, TCR, or IL-R – drive the downstream activation of RelA/p65 and p50. The nCP is stimulated by TNF superfamily receptors (TNFSFRs), including TNFSFR12A, lymphotoxin B receptors (LTBR), B cell-activating factor receptor (BAFF-R), receptor activator of NF-κB (RANK), CD40, and CD27. These receptors interact with specific ligands to drive downstream activation of RelB and p52.[133] The activation of the downstream signaling molecules is regulated by a group of kinases, including RIPK1, TBK1, and TBK1.[134] Following activation, signaling through the CP via downstream activation of RelA/p65 and p50 is regulated by RIP1, TBK1, and NIK;[133] however, for the nCP, NIK is the chief regulator of the downstream molecule, RelB/p52.[135] In the two pathways delineated (Figure 3), these kinases, consisting of IKKα, IKKβ, and IKKγ (NEMO), positively regulate the expression of inhibitors of kappa B kinases (IKK). While IKKα and IKKβ are the catalytic subunits of the complex, IKKγ is the regulatory subunit that is necessary for the activation of IKKβ of the CP or IKKα of the nCP.[134] It is worth mentioning that the activation of NF-κB is dependent on the IKKβ-mediated proteasomal processing of inhibitory kappa B alpha (IκBα) and p105, which sequester RelA and p50 in the cytoplasm of the CP.[136] Including IKKα-mediated proteasomal degradation of p100, which sequesters RelB in the cytoplasm of the nCP[137] under basal or unstimulated conditions, releasing RelA/p50 and RelB/p52, respectively, into the nucleus where they mediate NF-κB-dependent gene transcription.[133] Dysregulation of NIK, IKK complex, RIP1, and TBK1 has been attributed to the development of RA.[138–142] Studies have shown that alterations in these signaling nodes induce a permanent translocation of RelA/p50 and RelB/p52 and subsequent transcription of genes that regulate proinflammatory cells and soluble factors known to commit a healthy joint to chronic proliferation, hyperplasia, erosion, and destruction (reviewed in Makarov[143]).

Conventional drugs for RA treatment: success and limitation

We have delineated the signaling routes that promote the development of RA. Therefore, targeting signaling molecules that switch on RA pathways would be clinically relevant in reducing the burden of RA. Several candidate drugs have been developed to this effect. Disease-modifying antirheumatic drugs (DMARDs) are modern pharmacological therapies to treat and manage RA. These drugs are grouped into conventional synthetic DMARDs and biological DMARDs. The synthetic DMARDs are methotrexate, sulfasalazine, leflunomide/teriflunomide, and chloroquine/hydroxychloroquine. The mode of action of these drugs has been established. For instance, methotrexate – an analogue of folic acid inhibits purine and pyrimidine synthesis, transmethylation reactions, translocation of NF-κB to the nucleus, signaling via the Janus kinase JAK/STAT pathways and nitric oxide production and promotes adenosine release and expression of specific long-coding RNAs;[144] chloroquine/hydroxychloroquine – an immunomodulatory drugs interferes with lysosomal activity and autophagy, toll-like receptor (e.g. TLR7 and TLR9), and cyclic GMP-AMP (cGAMP) synthase (cGAS) activity, resulting in inhibition of cytokine production and modulation of specific co-stimulatory molecules (reviewed in Schrezenmeier and Dörner[145]); and sulfasalazine – an anti-inflammatory and immunomodulatory agent inhibits the expression of cyclooxygenase and PGE2, leukotriene production and chemotaxis, NF-κB activation, adenosine signaling, and proinflammatory cytokines (IL-1, IL-6, and TNF-α).[146] Biological DMARDs include antibody-based therapies, such as infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol, which target TNF-α and interfere with phagocytosis and production of proinflammatory cytokines, chemo-attractants, adhesion molecules and chemokine, function of Treg cells, osteoclasts, leukocytes, endothelial and synovial fibroblasts (reviewed in Kim and Moudgil[147]); rituximab, ofatumumab, belimumab, and atacicept which deplete and inhibit the functions of B cells via phagocytosis, Fc receptor gamma-mediated antibody-dependent cytotoxicity, complement mediated cell lysis, B cell apoptosis, and ablation of $CD4^+$ T cells;[148] abatacept and belatacept which

target CD80/86 and CD28/CTLA4 system triggering T cell tolerance (prevention of autoantigen recognition, immune cell infiltration, and T cell activation);[149] tocilizumab (anti-IL-6R),[150] anakinra, canakinumab, rilonacept (anti-IL-1)[151] and secukinumab (anti-IL-17)[152] suppress chronic inflammation in RA patients; densosumab and mavrilimumab which target growth and differentiation factors, such as RANKL and GC-CSF, respectively, and interfere with the maturation and activation of osteoclast (reviewed in Fassio *et al.*[153]), activation, differentiation, and survival of innates and adaptive cells, including macrophages, dendritic cells, neutrophils, T helper 1/17 cells, and modulation of pain pathways;[154] and small molecules, such as tofacitinib, baricitinib, and filgotinib, which target the major signaling pathway in RA, JAK1 and 3, JAK 1 and 2 and JAK 1, respectively.[155] Despite reported beneficial clinical evidence attributed to these pharmacological therapies, toxicities still abound to date. Included in the list are hepatotoxicity, retinopathy, cardiotoxicity, disorders of the CNS, skin, and blood, diarrhea and nausea, hypo-gamma-globulinemia, late onset of neutropenia, malignancy, severe/anaphylactoid transfusion reaction, increased serum cholesterol, low blood calcium and phosphate, and infections such as pneumonia and atypical tuberculosis, nasopharyngitis, candidiasis, and Zoster infection (rev in Guo *et al.*[156]). Thereby raising concerns about whether substances derived from plant botanicals could effectively prevent the development of RA or reduce the toxicities associated with RA conventional therapies?

Complementary and alternative medicine: potential elixirs for RA

Complementary and alternative medicine (CAM), otherwise known as an unorthodox health approach, involves the use of nutritional, consisting of medicinal plants and herbs, phytochemicals, antioxidants, special diets, dietary supplements, probiotics, and microbial-based therapy;[157–159] physiological, including hypnosis, meditation, prayer/spirituality, music, and relaxation therapy; physical, comprising massage, acupuncture, and spinal manipulation;[160,161] and combination of physiological and physical approaches, such as dance, yoga, tai chi, and art therapy, or a variety of nutritional and physiological processes, such as mindful eating to treat and manage diseases and infections.[27,162] CAM is self-prescribed and administered by patients without the assistance of health care providers or physicians.[163] It can be complementary or alternative medicine that uses conventional and unorthodox medicinal approaches or only an unorthodox medical approach. Presently, medicinal plants and herbs as alternatives to traditional therapy, or a combination of both therapeutics, are being integrated into the health system.[164,165] These natural resources contain chemicals called phytochemicals known to confer several medicinal benefits when taken by humans and animals.[166] There are 78,522 articles on medicinal plants published between 1787 and 2022 in PubMed only, indicating the rising interest in medicinal plants as an alternative to or in combination with conventional medicine. Medicinal plants and herbs can be administered in different forms to patients and are generally safe, easily accessible, and compatible with the animal's biochemical pathways and physiological functioning.[167–169] With the abundant ethnomedicinal claims attributed to CAM use in the world, there is the possibility that biologics derived from plant-based resources may replace conventional therapies or use as detoxifiers to reduce the toxicities associated with conventional treatments in the future. This claim is currently being debated. Some authors argued that plant-based medicine contains high levels of heavy metals, including arsenic, cadmium, mercury, and lead which may interfere with the therapeutic effect of the products and may induce disease state long term.[170,171] However, proper screening of plant-based products using high throughput chromatographic techniques will curb some clinical issues associated with using medicinal plants and herbs as CAM in the health system.[172]

Current evidence shows that the utilization of plants by man is beyond the fight against hunger and as a source of raw materials for industries. The relevance of plants has now been extended to the health system, and this is due to the abundant secondary metabolites, including alkaloids, tannins, saponins, flavonoids, phenols, polyphenols, terpenes/terpenoids, and steroids resident in medicinal plants.[173,174]

Indigenous Nigerian medicinal plants whose bioactive compounds possess anti-RA potential

CAM practitioners have unknowingly taken advantage of these bioactive compounds in Nigeria and reported some ethnomedicinal benefits against various disorders, including RA. Many of these plants (Figure 4 and Table 1) are prescribed by Nigerian traditional healers to treat and manage debilitating diseases, including RA, based on anecdotal claims passed on to them by their ancestors. Before now, this procedure of treating RA in Nigeria was questioned and clinically disapproved. However, current experimental findings reveal that certain bioactive compounds in plants may be responsible for the folk knowledge held by Nigerian traditional healers. Interestingly, some of the bioactive compounds target RA at the cellular level (cl) through the inhibition of the intracellular pathway (ip), and suppression of the generation of soluble factors (sf) (Table 2 and Figures 5 to 9).

Zingiber officinale is a commonly used household condiment. Spectral analytical findings reveal that *Z. officinale* contains abundant secondary metabolites, including alkaloid, phlobatannins, flavonoids, glycosides, saponins, tannins, and terpenoids, and further characterization using gas chromatography–mass spectrometry reveals specific bioactive compounds, such as α-Zingiberene, β-Sesquiphellandrene, α-Curcumin, Cyclohexane, α-Farnesene, cis-6-Shagole, gingerol, 2,6,10-Dodecatrien-1-ol, ϒ-Cadinene 6-dehydrogingerdione, gingerenone-A, gingerol, paradol, shogaol, zingerone, trans-1,8-cineole-3,6-dihydroxy-3-O-β-d-glucopyranoside, trans-3-hydroxy-1,8-cineole-O-β-d-glucopyranoside, and many more.[175,211,212] The anti-RA effect of some of these bioactive compounds has been demonstrated in experimental studies. The administration of ginger essential oils, chiefly 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol (28 mg/kg/d i.p.), inhibited PGE_2 production *in vitro* ($IC_{50} = 0.07$ µg extract/mL), thereby preventing SCW-joint swelling.[175] In addition, co-treatment with 6-gingerol suppressed osteoclast differentiation in co-cultures of osteoblasts and osteoclast

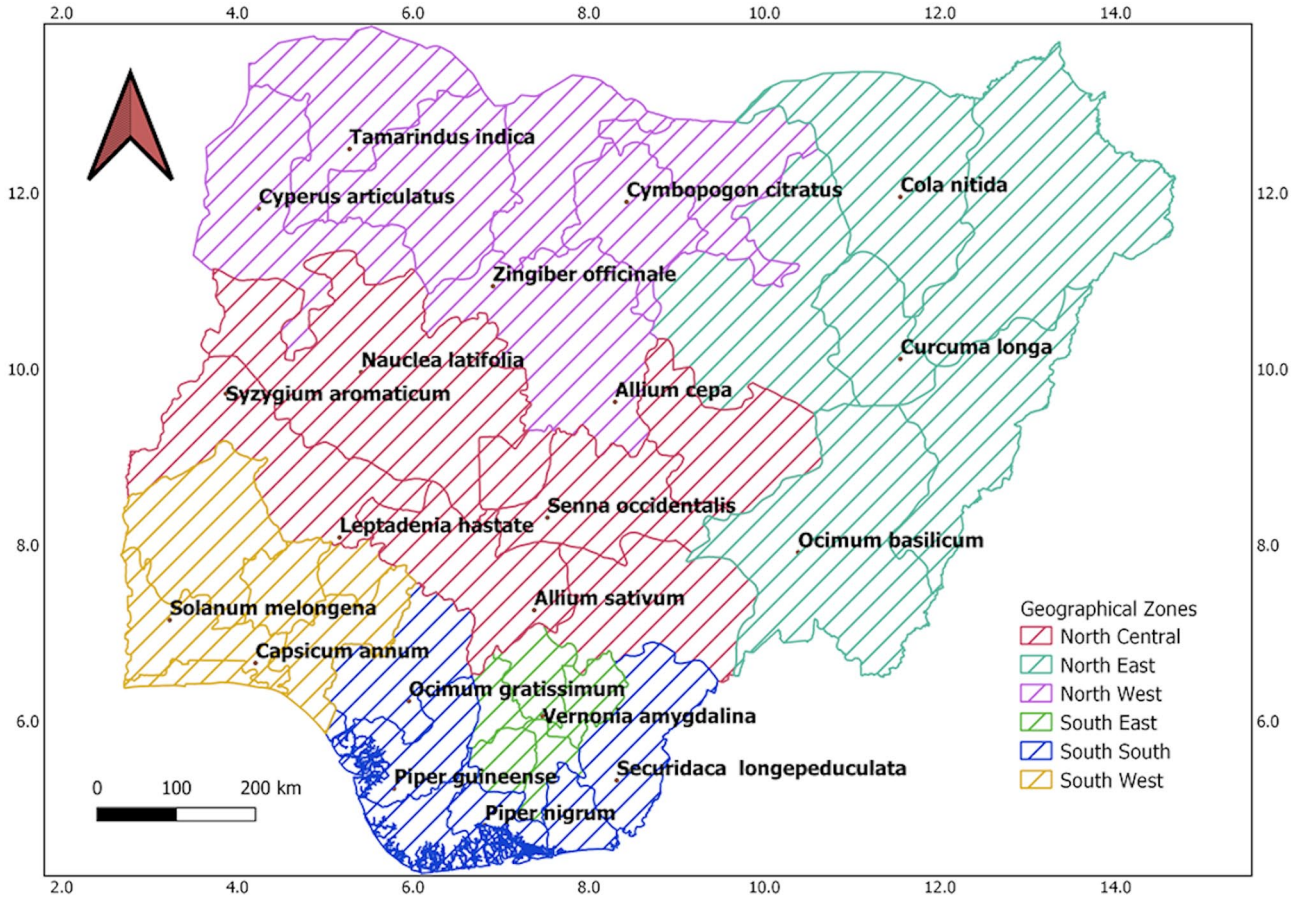

Figure 4. Map of Nigeria showing the distribution of included indigenous plants and herbs across the six geopolitical zones. (A color version of this figure is available in the online journal.)

Table 1. Indigenous Nigeria medicinal plants used in herbal setting for RA treatment.

S/N	Plant (Family)	Common name	Part used	Bioactive compound with anti-RA effect
1	*Zingiber officinale* (*Zingiberaceae*)	English – Ginger Hausa – Ata-ile Igbo – Chita Yoruba – Jinja	Rhizome	[6]-Gingerol [8]-Gingerol [10]-Gingerol [6]-Shogaol
2	*Allium cepa* (*Zingiberaceae*)	English – Onions Hausa – Yabasi Igbo – Alubosa Yoruba – Alubosa	Scale	Quercetin
3.	*Curcuma longa* (*Zingiberaceae*)	English – Tumeric Hausa – Gangamau Igbo – Yoruba – Ata-ile pupa	Rhizome	Curcumin
4.	*Cymbopogon citratus*	English – Lemon grass Hausa – Tsauri Igbo – Nchanwu Yoruba – Koriko-oba	Leaves	geranial (*trans*-citral) and neral (*cis*-citral)
5.	*Syzygium aromaticum* (*Myrtaceae*)	English – Clove Hausa – Kanafuru Igbo – Osaragbogo-eze Yoruba – konofuru	Oil	Eugenol
6	*Cassia/Senna occidentalis* (*Fabaceae/Leguminosae*)	English – Stink weed/Negro Coffee Hausa – Dora rai Igbo – Akidi agbara Yoruba – ewe oriesi	Leaves	Apigenin
7	*Nauclea latifolia* (*Rubiaceae*)	English – Pin cushion tree/African peach Hausa – Tabasiya Igbo – Ubulu inu Yoruba – Egbo egbesi	Root Stem Leaves	Caffeic acid

(Continued)

Table 1. (Continued)

S/N	Plant (Family)	Common name	Part used	Bioactive compound with anti-RA effect
8	*Ocimum basilicum* (*Lamiaceae*)	English – Scent leaf/basil Hausa – daidoya	Leave	Rutin (Vitamin P)
9	*Cyperus articulatus* (*Cyperaceae*)	English – Tiger nut Hausa – Aya Igbo – aki Hausa or Imumu Yoruba – Ofio	Rhizomes	α-pinene β-Caryophyllene oxide
10	*Tamarindus indica* (*Fabaceae*)	English – Tamarind/Tsamiya Hausa – tsamyia Igbo – icheku Yoruba – ajagbon	Seed	Threo-Isocitric acid Galactosyl glycerol, Procyanidin B2, Arecatannin B1, catechin, rutin, embelin
11	*Securidaca longepedunculata* (*Polygalaceae*)	English – Rhodesian violet Hausa – uwar magunguna, sanya Igbo – ezeogwu Yoruba – Ipeta	Root	Chlorogenic acid
12.	*Piper guineense* (*Piperaceae*)	English – Ashanti pepper Hausa – masoro Igbo – uziza Yoruba – iyere	Seed	Piperine
13	*Leptadenia hastate* (*Asclepiadaceae*)	English – Saltbush Hausa – Yadiya Igbo – isanaje Yoruba – iranaji	Leaves	Lupeol
14	*Piper nigrum* (*Piperaceae*)	English – Black pepper Hausa – masoro Igbo – uziza Yoruba – yawe-Dudu	Fruit	Piperine β-caryophyllene
15	*Allium sativum* (*Amaryllidaceae*)	English – Garlic Hausa – Tafarunua Igbo – Ayo-ishi Yoruba – Aayu	Bulb	Diallyl sulfide
16	*Cola nitida* (*Malvaceae*)	English – Kolanut Hausa – Gworo Igbo – Oji Yoruba – Obi gbanja	Bark	Stigmasterol
17	*Vernonia amygdalina* (*Asteraceae*)	English – Bitter leaf Hausa – shiwaka Igbo – olugbu Yoruba – ewuro	Leaves	Caffeoylquinic acids
18	*Ocimum gratissimum* (*Lamiaceae*)	English – Clove basil/African basil Hausa – Dadoya Igbo – Nchanwu Yoruba – Efirin-nla	Leaves	Eugenol
19	*Solanum melongena* (*Solanaceae*)	English – Eggplant Hausa – Dauta Igbo – Afufa Yoruba – Igbagba	Fruit	Apigenin
20	*Capsicum annuum* (*Solanaceae*)	English – Small chili pepper Hausa – Tatashi Igbo – Ose Yoruba – Atawewe	Fruit	Capsaicin

precursor cells in response to IL-1, inhibited IL-1-induced RANKL expression in osteoblasts. The addition of RANKL to the co-cultures annulled 6-gingerol-mediated inhibition of osteoclast differentiation, suppressed IL-1-induced PGE_2 production in osteoblasts. Adding exogenous PGE_2 overcame 6-gingerol-mediated inhibition of IL-induced RANKL expression in osteoblasts and osteoclast differentiation in the co-cultures. It suppressed the enzymatic activities of cyclooxygenase and PGE synthase, which cooperatively catalyze the conversion of arachidonic acid to PGE_2.[176]

Allium cepa is a commonly used condiment with known ethnopharmaceutical benefits. Ethnomedicinal records revealed that the *A. cepa* is rich in bioactive compounds, including quercetin, cycloalliin, S-methyl-L-cysteine, S-propyl-L-cysteine sulfoxide, dimethyl trisulfide, S-methyl-L-cysteine sulfoxide, and N-acetyl cysteine.[213] The anti-RA activity of some of these bioactive compounds has been evaluated experimentally. Anti-RA effect of quercetin was assessed in rats challenged with complete Freund adjuvant (CFA) and the following RA parameters, arthritis scores, paw edema, latency, activities of myeloperoxidase (MPO), ecto-nucleoside triphosphate diphosphohydrolase (E-NTPDase), and ectoadenosine deaminase (E-ADA) in lymphocytes were measured. The treatment with quercetin at the doses

Table 2. Bioactive compounds identified from the reviewed medicinal plants and herbs and their possible effects on the pathophysiology of RA.

S/No.	Bioactive compound	Concentration	Effect on pathophysiology of RA	Reference	Therapeutic target
1	[6]-Gingerol [8]-Gingerol [10]-Gingerol [6]-Shogaol	28 mg/kg	Inhibition in the PGE_2 production *in vitro* (IC_{50} = 0.07 μg extract/mL). Prevention of SCW-induced joint swelling.	175	sf
	[6]-Gingerol	1.25–10 μM	Inhibition in IL-1-induced RANKL expression in osteoblast. Suppression of IL-1-induced PGE_2 production in osteoblast. Reduction in the activity of COX-2 and PGE synthase.	176	Ip sf
2	Quercetin	5, 25, and 50 mg/kg	Attenuation of the purinergic system (E-NTPDase and E-ADA activities) and the levels of IFN-gamma and IL-4.	177	sf
		25 mg/kg	Reduction in leukocytosis and immune expression of TNF-α, IL-17 in the synovial membrane.	178	sf
		50 nmol/L	Inhibition in the production of proinflammatory cytokines (IL-1β, IL-6, and IL-8) and expression of XIST in RA-FLS treated with TNF-α.	179	sf ip
3.	Curcumin	0–10 μM	Inhibition in the number of osteoclasts generated in a dose-dependent manner. Reduction in RANK mRNA and protein expression levels in a dose-dependent manner. Suppression in the protein expression levels of c-Fos and NFATc1 in a dose-dependent manner.	180	ip
		1 2.5–10 μM	Inhibition in IL-6 expression induced by IL-1β and PMA. Blocking in VEGF-A expression induced by PMA in a concentration-dependent manner.	181	sf ip
4.	Geranial (*trans*-citral) and neral (*cis*-citral)	10 mg/kg,	Reduction in carrageenan-induced paw edema and croton-induced acute ear edema.	182	cl
		3–12 μg/mL	Inhibition in iNOS, NO production, NF-κB pathway, and IκB phosphorylation in RAW 264.7 cells.	183	sf ip
		0.001% 0.002% 0.004%	Suppression of LPS-induced COX-2 promoter activity and activation of PPARα and γ.	184	Ip
5.	Eugenol	100 μg	Inhibition in mononuclear cell infiltration into the knee joints of arthritic mice. Suppression in the levels of cytokines TNF-α, IFN-γ, and TGF-β within the ankle joints.	185	cl sf
		0.1 μM	Inhibition of LPS-stimulated NF-κB activation, cytokine release (TNF-α, IL-1β, and CXC chemokine), and COX-2 expression by macrophages *in vitro.*	186	ip sf
		10–20 mg/kg	Reduction in paw volume in CIA rats. Decrease ROS formation and levels of NO in CIA rats. Enhanced antioxidant levels and activities of GSH, SOD, GPx, GR, and CAT. A lower biomarker of oxidation including MDA, carbonyl groups, and DNA damage and proinflammatory cytokines: TNF-α and IL-6 in the plasma and joint of CIA rats.	187	cl sf
		2.5, 5, and 10 mg/kg	Suppress the infiltration of inflammatory cells. Inhibition of the activities of arginase, adenosine triphosphate, and adenosine monophosphate hydrolyze. Elevation of adenosine diphosphate hydrolysis and adenosine deaminase activities of carrageenan-induced arthritis rat model.	188	cf sf

(Continued)

Table 2. (Continued)

S/No.	Bioactive compound	Concentration	Effect on pathophysiology of RA	Reference	Therapeutic target
6	Apigenin	20 mg/kg bw	Inhibition of synovial hyperplasia through induction of fibroblast-like synoviocytes apoptosis. Repression of angiogenesis via downregulation of VEGF and VEGFR in CIA mouse Suppression of osteoclastogenesis-associated RANKL/RANK/OPG system in CIA mice.	189	cl ip
		0–100 μM	Induction of apoptosis through the activation of effectors caspase-3 and caspase-7 in RA-FLSs. Induction of ROS and oxidative stress-activated ERK1/2 in RA-FLSs.	190	Ip
7	Caffeic acid	50 mg/kg/day	Mitigated paw edema and histopathologic aberrations. Lowered the expression of paw NF-κB, CHI3L1, and IL-1β Suppressed paw MMP-9 and VEGF levels. Attenuated lipid peroxides and nitric oxide generations. Downregulated paw caspase-3 pro-apoptotic signal in an adjuvant-induced arthritis model.	191	cl sf ip
8	Rutin (Vitamin P)	100 μM	Inhibition in oxidative stress markers of NO and NADPH oxidase in the neutrophils and monocytes of RA patients.	192	sf
		1 mg/dose/mouse	Reduction in edema in *Candida albicans*-septic arthritis. Suppression of NO production from macrophages and T cells proliferation.	193	cl sf
		15 mg/kg	Reduction in paw diameter, infiltration of inflammatory cells, synovial hyperplasia, pannus formation, and cartilage and bone erosion in CFA-induced arthritic rats. Restoration of the antioxidant levels of SOD, GPx, and GSH while decreasing MDA level. Suppression in the expression of TNF-α and IL-1β, NF, and NF-κBp65.	194	cl sf ip
9	α-pinene	50, 100, 200 mg/kg	Alleviated CFA-induced hind paw volume. Decreased CFA-induced increase in ALT, ALP, TNF-α, NO, TBARS, H_2O_2 levels in the serum, liver, and ankle joint. Elevated CFA-induced increase in TAOC and GSH levels in the liver and ankle joint.	195	cl sf
	β-Caryophyllene oxide	75 mg/kg	Inhibited paw inflammation (%), clinical arthritic score, and bone and joint destruction in AIA rats. Suppressed the production of IL-1β and TNF-α AIA rats. Inhibited the expression of caspase-1p20 and IL-1β in ankle joint synovial tissues of AIA rats.	196	cl sf ip
10	Threo-Isocitric acid Galactosyl glycerol, Procyanidin B2, Arecatannin	50 mg/kg	Reverses paw swelling/volume in CFA-induced arthritis rats. Reduces the formation of pannus in CFA-induced arthritis rats. Inhibits the activities of hyaluronidase and MMP-2, -3, -9, and -13 in CFA-induced arthritis rats. Suppresses the activities of cathepsin K, N-acetyl hexosaminase, β-D-glucuronidase, cathepsin D, ALP, ACP, TRAP in CFA-induced arthritis rats. Retards the levels TNF-α, IL-1β, IL-6, IL-23, and COX-2 and increases the level of IL-10 in CFA-induced arthritis rats. Reduces arthritic-induced endogenous generation of ROS and hydroperoxides and sustains an intracellular level of GSH and expression level of SOD, CAT, and GST.	197	cl sf ip
11	Catechin	10–60 μM	Interferes with the IL-1β signaling pathway, which regulates the expression of proinflammatory mediators (IL-6 and IL-8) and Cox-2 in primary human RA synovial fibroblasts (RASFs). Inhibits IL-6, IL-8, and MMP-2 production and TAK1 (TBK1) activity.	198	ip sf
12	Embelin	25 and 50 mg/kg	Reduces arthritic score and paw swelling in CFA-induced hind paw. Reduces MDA and NO levels and restores the antioxidant level of SOD and GSH in CFA-induced hind paw. Downregulates the levels and expression of TNF-α, IL-6, and IL-1β and the expression of NF-kB in CFA-induced hind paw.	199	cl sf ip
13	Chlorogenic acid	20, 50, 80, and 100 μM	Attenuated arthritis progression and markedly inhibited BAFF and TNF-α production in serum. Inhibits TNF-α-induced BAFF expression. Reduces the DNA-binding activity of NF-κB to the BAFF promoter region and suppresses BAFF expression through the NF-κB pathway in TNF-α-stimulated MH7A cells.	200	sf ip
		5, 10, 25, 50 and 100 μmol/L	Inhibits the inflammatory proliferation of RSC-364 cells mediated by IL-6. Suppresses the expression levels of key molecules in the JAK/STAT and NF-κB signaling. Inhibits the activation of JAK/STAT and NF-κB signaling.		cl sf ip

(Continued)

Table 2. (Continued)

S/No.	Bioactive compound	Concentration	Effect on pathophysiology of RA	Reference	Therapeutic target
14.	Piperine	10–100 μg/mL	It suppressed the expression of IL-6 and MMP-13 and reduced the production of PGE_2 in a dose-dependent manner of IL-1β-stimulated FLS in rats.	201	sf
		10 mg/kg	Decreases carrageenin-induced rat paw edema and the weight of cotton pellet granuloma similar to oxyphenyl butazone – the reference drug. Protected against croton oil-induced granuloma pouch.	202,201	cl
15	Lupeol	42 mmol/ear	Inhibits croton-induced rat paw formation.	203	cl
		50 mg/kg	Suppresses the activities of lysosomal enzymes, such as β-glucuronidase, acid phosphatase, cathepsin D, and N-acetylglucosaminidase in the plasma, liver, kidney, and spleen in adjuvant-induced arthritis in rats. Decreases the levels of plasma protein-bound carbohydrates, including hexose, hexosamine, hexuronic acid, fucose, and sialic acid in adjuvant-induced arthritis in rats. Increases the collagen and urinary contents of hydroxyproline, hexosamine, hexuronic acid, glycosaminoglycan in adjuvant-induced arthritis in rats.	204	cl
15	β-caryophyllene	300 mg/kg	Reduces paw thickness and arthritic index and expression of TNF-α in adjuvant-induced arthritis in rats.	205	cl sf
16	Diallyl sulfide	100 mg/kg bw	Reduces paw edema and the levels of CRP in carrageenan-challenged arthritic rats. Suppresses the expression of TNF-α, IL-1β, L-2, iNOS, COX-2, NF-κB, and MPO, and the production of NO, PGE2, and MCP-1 in the injured paw tissue of in carrageenan-challenged arthritic rats. Increases the IL-10 and GSH in the injured paw tissue of carrageenan-challenged rats.	206	cl sf ip
17	Stigmasterol	200 mg/kg	Restrains the CIA-induced increase articular elastase activity in CIA rats. Suppresses the expression of TNF-α, IL-6, IL-1β, iNOS, and COX-2 in CIA rats. Downregulates the expression of NF-kBp65, and p38MAPK in joints in CIA rats. Upregulates the expression of IL-10 in CIA rats.	207	sf ip
18	Caffeoylquinic acids	300 mg/kg	Downregulates the expression of PGE2, NF-κβ, IL-1β, collagen type 10α1, and caspase3 monosodium iodoacetate-induced arthritis model in ovariectomized female rats. Upregulates the expression of the anti-inflammatory IL-10 and collagen type 2α1 mRNA expressions in monosodium iodoacetate-induced arthritis model in ovariectomized female rats.	208	ip sf
19	Eugenol	2.5, 5, and 10 mg/kg	Suppress the infiltration of inflammatory cells. Inhibition of the activities of arginase, adenosine triphosphate, and adenosine monophosphate hydrolyze. Elevation of adenosine diphosphate hydrolysis and adenosine deaminase activities of carrageenan-induced arthritis rat model.	188	cl sf
20	Apigenin	20 μM	Reduces joint swelling in CIA mice. Decreases the level of TNF-α, IL-1β, and IL-6 in CIA mice. Suppresses DC maturation during the acute phase of CIA. Inhibits the expression of CXCR4 on peripheral blood. Reduces the percentage of DCs in LNs and changes in the DC subset of LNs.	209	cl sf ip
21	Capsaicin	10^{-6} mol/L 10^{-8} mol/L	Induces the expression of collagenases from synoviocytes. Inhibits the synthesis of PGE_2.	210	sf

PMA: Phorbol 12-myristate 13-acetate; PPAR: Peroxisome proliferator-activated receptor; RA-FLSs: Rheumatoid arthritis fibroblast-like synoviocytes; OPG: Osteoprotegerin; NF-κB: Nuclear factor-kappa B; IL-1β: Interleukin 1-beta; TNF-α: Tumor necrosis factor-alpha; IL-6: Interleukin 6; IL-8: Interleukin 8; IL-17: Interleukin 17; Il-23: Interleukin 23; TGF-β: Transforming growth factor-beta; RANKL: receptor activator of nuclear factor-κB ligand; RANK: receptor activator of nuclear factor-κB receptor; CXC: Chemokines; iNOS: Inducible nitric oxide synthase; NO: Nitric oxide; VEGFA: Vascular endothelial growth factor ligand A; PGE_2: Prostaglandin E_2; COX-2: Cyclooxygenase 2; NFATC1: Nuclear factor of activated T cells 1; TRAP: Tartrate-resistant acid phosphatase; E-NTPDase: Ectonucleoside triphosphate diphosphohydrolase; E-ADA: ectoadenosine deaminase; XIST: short interfering (si)-X-inactive specific transcript; SCW: Streptococcal cell wall; IFN-γ: interferon-gamma; LPS: lipopolysaccharide; CIA: Collagen-induced arthritis; GSH: reduced glutathione; SOD: Superoxide ion dismutase; GPx: Glutathione peroxidase; GR: Glutathione reductase; CAT: catalase; MMPs: Matrix metalloproteinases; NADPH: reduced Nicotinamide adenine dinucleotide phosphate; MDA: Malondialdehyde; CFA: Complete Freund's adjuvant; ALT: Alanine amino transferase; ALP: Alkaline phosphatase; TBARS: Thiobarbituric acid reactive substance; TAOC: Total antioxidant capacity; ACP: Acid phosphatase; GST: Glutathione S-transferase; TAK1: TGF-β activated MAP kinase; MCP-1: Monocyte chemoattractant protein-1; LN: lymph nodes; C: Cell; IP: Intracellular pathways; SF: Soluble factors.

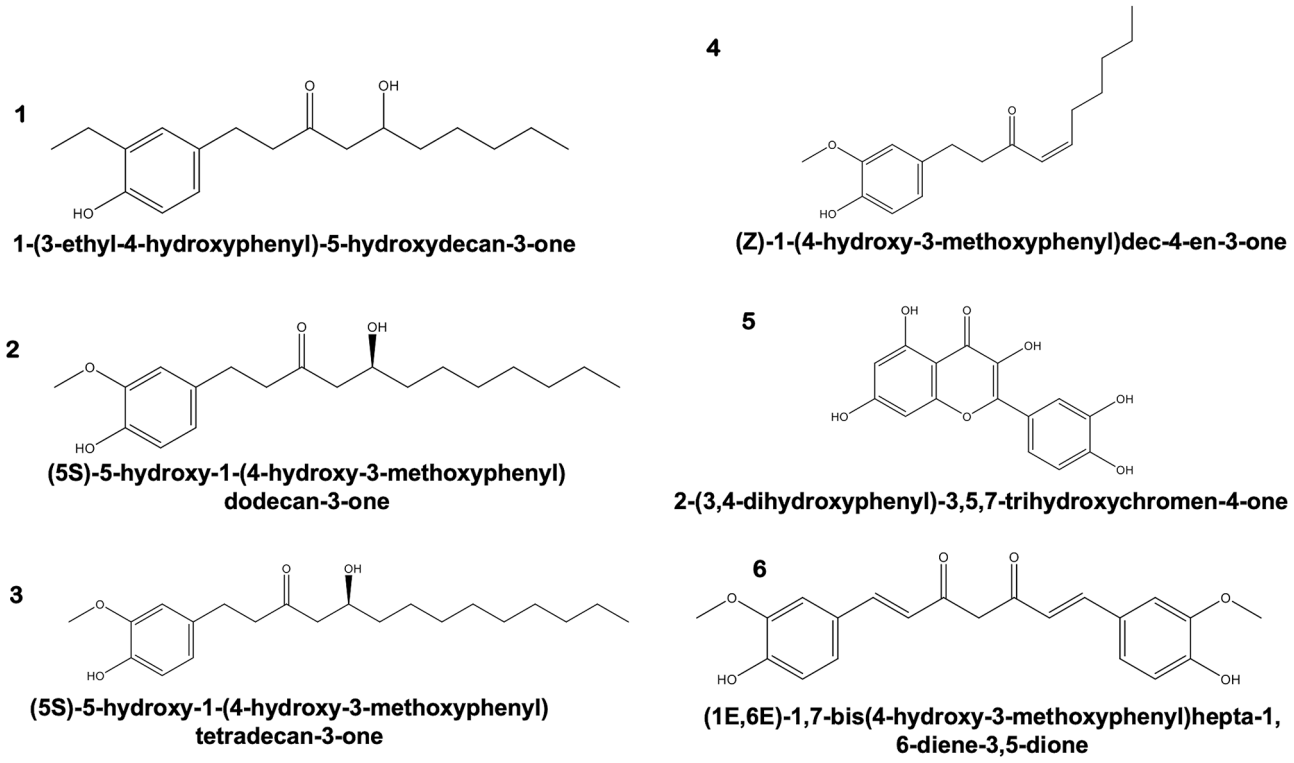

Figure 5. Chemical structures of some bioactive compounds identified from the reviewed medicinal plants: 1. 6-Gingerol, 2. 8-Gingerol, 3. 10-Gingerol, 4. 6-Shogaol, 5. Quercetin, 6. Curcumin. *The scheme was modeled with ChemDraw.*

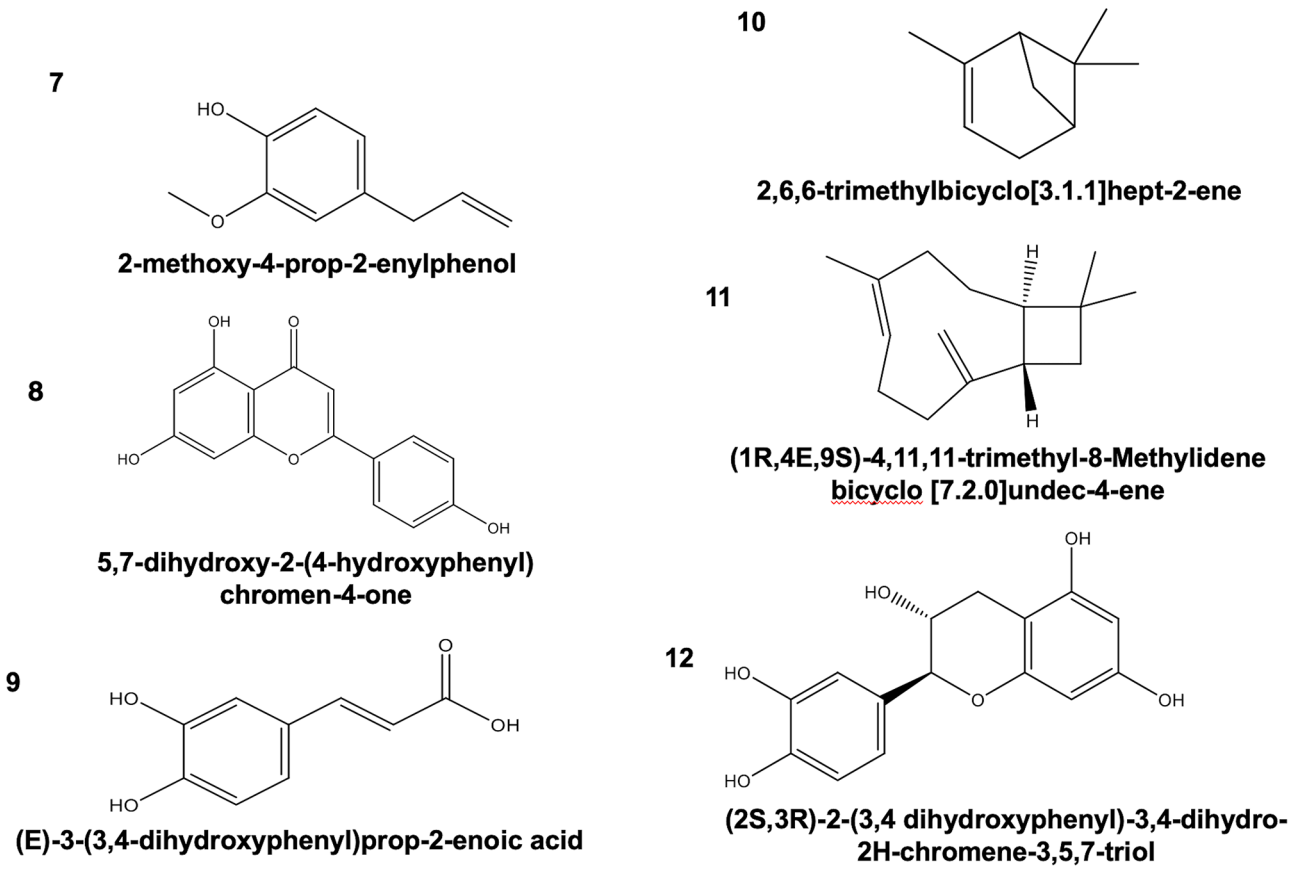

Figure 6. Chemical structures of some bioactive compounds identified from the reviewed medicinal plants: 7. Eugenol, 8. Apigenin, 9. Caffeic acid, 10. α-Pinene, 11. β-Caryophyllene, 12. Catechin. *The scheme was modeled with ChemDraw.*

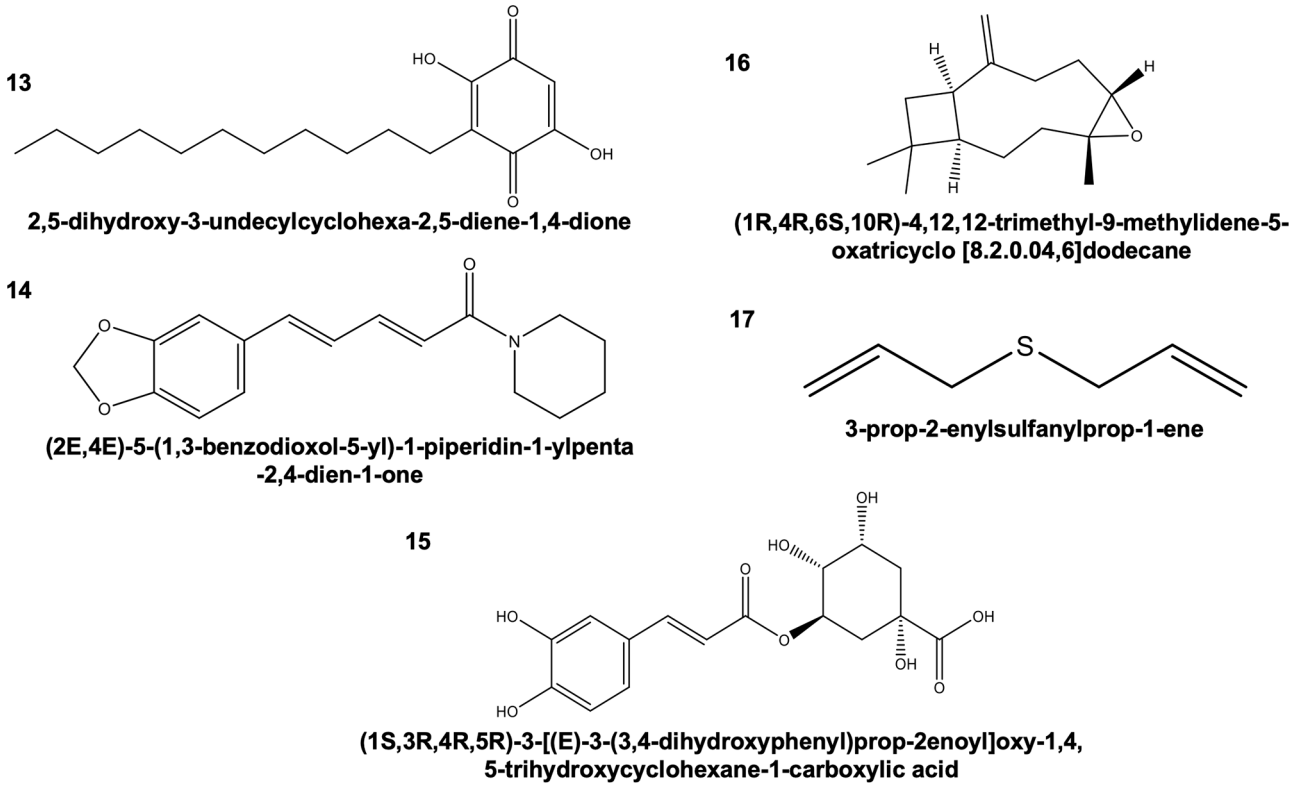

Figure 7. Chemical structures of some bioactive compounds identified from the reviewed medicinal plants: 13. Embelin, 14. Piperine, 15. Chlorogenic acid, 16. β-Caryophyllene oxide, 17. Diallyl sulfide. *The scheme was modeled with ChemDraw.*

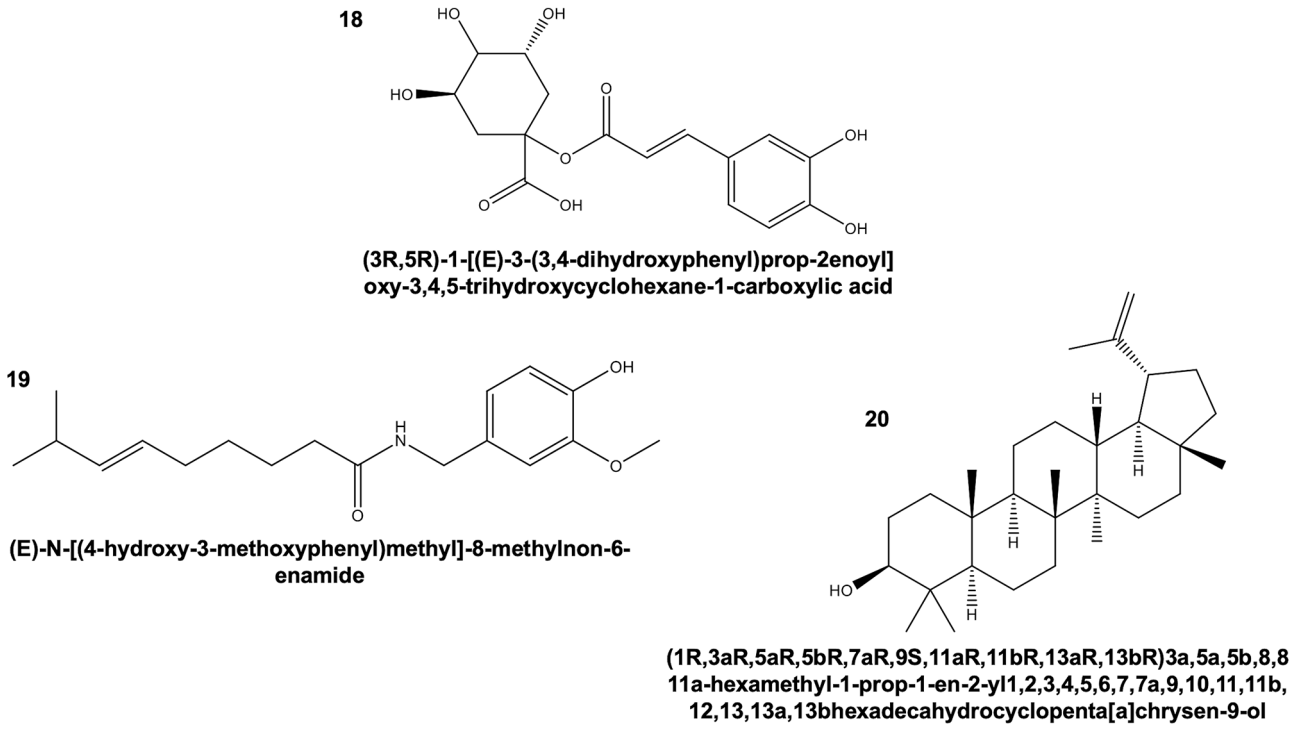

Figure 8. Chemical structures of some bioactive compounds identified from the reviewed medicinal plants: 18. Caffeoylquinic acid, 19. Capsaicin, 20. Lupeol. *The scheme was modeled with ChemDraw.*

of 5, 25, and 50 mg/kg post 45 days significantly reduced arthritic score and paw edema, infiltration of inflammatory cells, activities of MPO and E-NTPDase, serum levels of adenosine, and cytokine levels (IFN-gamma and IL-4).[177] In another study, RA induced in rats with three intra-articular injections of methylated bovine serum albumin (1×/week)

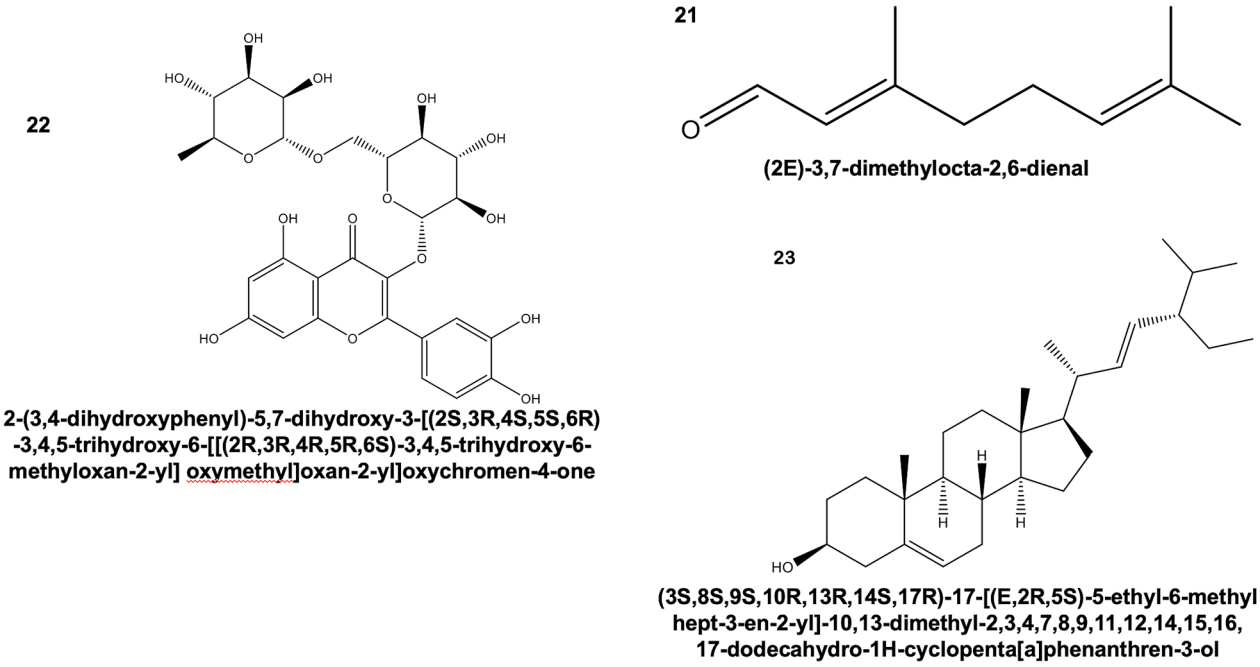

Figure 9. Chemical structures of some bioactive compounds identified from the reviewed medicinal plants 21: Citral, 22: Rutin, 23: Stigmasterol. *The scheme was modeled with ChemDraw.*

in the temporomandibular joint (TMJ), quercetin (25 mg/kg) significantly reduced the nociceptive threshold ($P < 0.001$) and decreased leukocyte recruitment in synovial fluid ($P < 0.001$), intense inflammatory infiltrate ($P < 0.001$), and intense immunoexpression of TNF-α, IL-17, and IL-10 in the synovial membrane ($P < 0.001$) and reversed hepatotoxicity associated with methotrexate used in the treatment of RA.[178] The treatment of TNF-α-mediated RA fibroblast-like synoviocytes (RA-FLSs) with quercetin (50 nmol/L) for 2 h inhibited the production of proinflammatory cytokines (IL-1β, IL-6, and IL-8) and expression of short interfering (si)-X-inactive specific transcript (XIST).[179]

Curcuma longa is a vital food condiment commonly found in many Nigerian homes. It contains beneficial bioactive compounds, such as digalloyl-hexoside, caffeic acid hexoside, curdione, coumaric, caffeic acid, sinapic acid, quercetin-3-D-galactoside, casuarinin, bisdemethoxycurcumin, curcuminol, demethoxycurcumin, isorhamnetin, valoneic acid bilactone, curcumin, and curcumin-O-glucuronide.[214] Curcumin has been evaluated for its anti-RA effect, one of the most active phytoconstituents. In an attempt to determine the effect of curcumin on the osteoclastogenic potential of peripheral blood mononuclear cells (PMBCs) collected from RA patients, Shang *et al.*[180] demonstrated that the treatment with curcumin (0–10 μM) inhibited PMBC-mediated osteoclastogenesis by suppressing the activation of extracellular signal-regulated kinases 1 and 2, p38, and c-Jun N-terminal kinase and inhibiting receptor activator of nuclear factor κB (RANK), c-Fos, and nuclear factor of activated T cells (NFATc1) expression. The effect of curcumin on the human synovial fibroblast cell line MH7A and fibroblast-like synoviocytes (FLS) derived from patients with RA was evaluated. Interestingly, treatment with curcumin (2.5–10 μM) effectively blocked IL-1β and PMA-induced IL-6 expression both in MH7A cells and RA-FLS, inhibited the activation of NF-κB, and induced dephosphorylation of ERK1/2 and blocked the expression of VEGF-A induced by PMA in a concentration-dependent manner.[181]

Cymbopogon citratus is a medicinal plant with abundant ethnomedicinal properties. Analysis of the essential oil found in *C. citratus* using trace gas chromatographic (GC) Thermo Quest system equipped with FID and a DB-5 column revealed a total of 16 chemical constituents with Geranial (trans-citral; 27.04%), neral (cis-citral; 19.93%), and myrcene (27.04%) being the major constituents.[215] Treatment with *C. citratus* essential oil rich in geranial and neral (10 mg/kg, administered orally) significantly reduced carrageenan-induced paw edema (a model of RA) like that observed for oral diclofenac (50 mg/kg), which was used as the positive control. In mice treated with croton oil, citral-rich extract at 5 and 10 μL/ear markedly decreased acute ear edema.[182] In another study, citral (3–12 μg/mL) significantly inhibited LPS-induced NO production, transcriptional activity, and expression of iNOS, DNA-binding activity, and nuclear translocation of NF-κB and IκB phosphorylation in RAW 264.67 cells.[183] Citral at a concentration of 0.001%, 0.002%, and 0.004% was found to suppress the activity of COX-2 and activate PPARα and γ. In human macrophage-like U937 cells, citral dose-dependently inhibited both LPS-induced COX-2 mRNA and protein expression and induced the mRNA expression of the PPARα-responsive carnitine palmitoyltransferase one gene and the PPARγ-responsive fatty acid-binding protein four gene, suggesting that citral activates PPARα and γ, and regulates COX-2 expression.[184]

Syzygium aromaticum is another excellent plant resource replete with essential oil. Spectral analysis of essential oils from *S. aromaticum* revealed several beneficial bioactive compounds, including eugenol, β-caryophyllene, vanillin,

crategolic acid (maslinic acid), kaempferol, rhamnetin, eugenitin, eugenin, ellagic acid, gallic acid, biflorin, myricetin, campesterol, stigmasterol, oleanolic acid, quercetin, carvacrol, α-pinene, limonene, p-cymene, 1,8-cineole, phenethyl alcohol, benzyl acetate, methyl chavicol, α-terpineol, linalyl acetate, and nerol.[216,217] Of these bioactive, eugenol is the most predominant, with a relative abundance of 90.45% in *S. aromaticum*. In collagen-induced arthritis (CIA) model to investigate the potential role of eugenol in the management of human arthritis, eugenol (100 μg) suppressed mononuclear cell infiltration into the knee joints of arthritic mice. It decreased cytokine levels of TNF-α, IFN-γ and TGF-β.[185] In addition, eugenol exhibited an antiarthritic effect in the collagen-induced RA model by reducing paw volume, decreasing ROS formation, NO generation and biomolecular oxidation level of MDA, carbonyls and DNA damage, elevating antioxidant levels and activities of GSH, SOD, GPx, GR and catalase as well as suppression the expression of proinflammatory cytokines TNF-α, IL-6 with a concomitant increase in anti-inflammatory cytokine, IL-10.[187] Treatment with eugenol and isoeugenol (0.1 μM) further inhibited LPS-stimulated NF-κB activation, cytokine release (TNF-α, IL-1β, and CXC chemokine), and COX-2 expression in RAW264.7 murine macrophages.[186]

Sennia occidentalis (Syn. *Cassia occidentalis*) is replete with the following bioactive compounds including Apigenin, 4-Methoxy-2′,4′-dihydroxy chalcone, 4′,7-Dihydroxy flavone, Luteolin, 3′,4′,7-Trihydroxy-flavone, Emodin, Nicotinic acid, Chrysophanol 1-*O*-β-Gentiobioside, Rhamnocathartin and Isovitexin[218] with apigenin being the most active phytoconstituent whose antiarthritic effect has been illustrated experimentally. Apigenin, a plant flavone, is known to exert an antiarthritic effect. In the collagen-induced arthritis (CIA) mouse model, apigenin (20 mg/kg bw) protected the mice against RA in a dose- and time-dependent manner by repressing CIA-induced increase in the arthritic index (AI) score, decreased CIA-induced increase in synovial hyperplasia, inflammatory cell infiltration, dilation, and congestion in the blood vessels and pannus. Fluorescence-activated cell sorting (FACS) analysis of the FLS revealed that Apigenin mediated its antiproliferative tendency by decreasing the G1 phase and G2/S phase cell numbers, thereby slowing cell cycle progression while elevating apoptosis in FLS as indicated by Annexin V (AV)-PI staining. In addition, apigenin further decreased angiogenesis by repressing the expression of VEGF, VEGFR 1, and VEGFR2 and suppressed the activation of osteoclast by inhibiting the expression of RANKL and RANK while upregulating the expression of osteoprotegerin (OPG). The binding of VEGF to its receptor VEGFR is central to angiogenesis and the formation of pannus in RA.[219] RANKL interacts with the RANK receptor on osteoclast precursors and drives osteoclastogenesis[220] – an essential hallmark in the development of RA. OPG acts as a decoy receptor by preventing the binding of RANK to RANKL.[221] Therefore, apigenin exerts its antiarthritic effect and RANKL/RANK/OPG system in CIA mice, thus making it a putative candidate for RA treatment with low toxicity.[189] In another study, treatment of human RA-FLSs with apigenin (0–100 μM) increased survival rate, increased the generation of reactive oxygen species (ROS), and increased the expression of caspase-3 and caspase-7 (a marker of apoptotic cell death) via the activation of the MAPK and phosphorylation of ERK1/2 in RA-FLSs.[190]

Nauclea latifolia contains different phytochemicals, such as saponins, flavonoids, alkaloids, cardiac glycosides, terpenoids, tannins, and phenolic compounds.[222] Further characterization of the extract of *N. latifolia* revealed numerous bioactive compounds, including strictosamide, naucleamides A, naucleamide F, quinovic acid-3-O-beta- rhamnopyranoside, quinovic acid 3-O-beta-fucosylpyranoside,[223] quercetin, quercetin-3-O-β-glycopyranoside, 3-caffeoylquinic acid (chlorogenic acid), trans-3,4-dihydroxycinnamic acid (Caffeic acid), and 3,5-O-dicaffeoylquinic acid.[224] The administration of crude stem bark extract of *N. latifolia* (150 and 300 mg/kg) decreased CFA-induced increased paw thickness in female Wistar Albino rats and reduced the level of NO and lipid peroxidation (TBARs), activities of arginase, angiotensin-converting enzyme (ACE), adenine deaminase, acetylcholinesterase, and butyrylcholinesterase, and the hydrolysis of adenosine triphosphate and adenosine monophosphate in the platelets of complete CFA-induced arthritic rats.[225] The antiarthritic potential of *N. latifolia* is attributed to the bioaccumulation of essential bioactive compounds with known anti-inflammatory functions. For instance, in an adjuvant-induced arthritic model of adult male Sprague-Dawley rats, the administration of caffeic acid (50 mg/kg/day) for 20 days mitigated paw edema and inflammatory cell infiltration and protected the joint tissues against pannus formation along with cartilage and bone destruction. Interestingly, caffeic acid also lowered the paw expression of NF-κB and the downstream effector CHI3L1 and its synthesis inducer IL-1β, decreasing the tissue remodeling factor MMP-9 and the angiogenic signal VEGF in rat paws.[191]

Ocimum basilicum is an aromatic herb used in folk medicine for the treatment of inflammatory disorders owing to the abundance of bioactive compounds, including rutin, epicatechin, vanillic acid, gallic acid, 3,4-dihydroxy benzoic acid, 4-dihydroxy benzoic acid, 2,5-dihydroxy benzoic acid, chlorogenic acid, p-coumaric acid, ferulic acid, ellagic, naringin, cinnamic acid, quercetin and caffeic acid with rutin, epicatechin, and vanillic acid having the highest relative abundance (%).[226] Others, such as linalool, methyl chavicol, α-epi-Cadinol, eugenol and γ-cadinene, were also identified in the fresh and dry leaves of *O. basilicum*.[227] The antiarthritic potential of *O. basilicum* is yet to be established. Still, recent findings reveal that the plant confers anti-inflammatory functions in obese patients – a risk factor for RA. They reported that the administration of 3T3L1 adipocytes seeded with RAW264.7 macrophages with 5 and 25 mg μg/mL. *O. basilicum* for 24 h reduced the expression of inflammatory cytokine mRNA, including Il-16, IL-1β, TNF-α, and CCL2 and inhibited the expression of NF-κB – a transcription factor of inflammatory cytokines, and co-stimulatory CD137 (Tnfrsf9)/CD137L inflammatory signaling.[228] The antiarthritic effect of some of the bioactive compounds identified in a different part of *O. basilicum* has been established in experimental studies. Rutin, otherwise known as vitamin P, is the most abundant polyphenolic flavonoid widely distributed in *O. basilicum*. Empirical evidence revealed that the treatment of neutrophils and monocytes isolated from the

leukocytes of RA patients with rutin (100 μM) suppresses oxidative stress via the reduction of NO production and activity of NADPH oxidase.[192] Another study investigating the antiarthritic effect of rutin was *Candida albican*-induced septic arthritis in BALB/c mice. The findings show that the administration of rutin (1 mg/dose/mouse, i.p.) for 17 days reduced approximately 45% of edema at the peak day (Day 11) of septic arthritis ($P < 0.05$) inhibited NO production from macrophages and T cells proliferation and inhibited the growth of *C. albican* yeast cells ($P < 0.01$).[193] Furthermore, rutin (15 mg/kg) reduced paw diameter, infiltration of inflammatory cells, synovial hyperplasia, pannus formation, and cartilage and bone erosion in CFA-induced arthritic rats, restored the antioxidant levels of SOD, GPx, and GSH levels with a concurrent decrease in MDA level, and suppressed the expression of TNF-α and IL-1β, NF, NF-κB p65, and NF-κBp65 (Ser536).[194]

Cyperus articulatus extracts are used in different parts of Nigeria to treat diseases and infections. Chemical analysis of its rhizomes revealed a total of 42 essentially oils belong to hydrocarbon monoterpenes, oxygenated monoterpenes, hydrocarbon sesquiterpene, and oxygenated monoterpene with muskatone (11.60%), cyclocolorenone (10.30%), α-pinene (8.26%), pogostol (6.36%), α-copaene (4.83%), and β-caryophyllene oxide (4.82%) being most abundant bioactive compounds using chloroform as extraction solvent.[229] In another study, corymbolone (14.25%), cyclocolorenone (9.75%), cadalene (8.36%), hexadecanoic acid ethyl ester (5.99%), 9-octadecenoic acid ethyl ester (5.5%), cholesta-3,5-diene (4.82%), and cis-thujopsenal (4.19%) were considered most abundant in the rhizome of *C. articulatus* residue using ethanol as a solvent for extraction.[230] To the best of our knowledge, there is no information in the pharmacopeia showing the anti-RA effect of *C. articulatus* extract or specific bioactive compound identified in the plant despite anecdotal claims among CAM practitioners and users. However, two active compounds, α-pinene and caryophyllene oxide, have been shown to protect Eugenia aquea and Liquidambaris fructus against adjuvant-induced RA significantly. Specifically, α-pinene-rich *E. aquea* at 50, 100, and 200 mg/kg alleviated CFA-induced hind paw volume and other complications observed in arthritic rats; decreased the levels of ALT, ALP, TNF-α, and NO while elevating total antioxidant capacity (TAOC) in the serum of arthritic rats; retarded the levels of TBARS and hydrogen peroxide (H_2O_2) with a concomitant increase in reduced GSH of arthritic rats.[195] β-caryophyllene oxide screened from the petroleum ether extract of *L. fructus* was observed to confer a protective effect against adjuvant-induced RA in rats by inhibiting paw inflammation (%), clinical arthritic score, and bone and joint destruction in AIA rats; suppressed the production of IL-1β and TNF-α in; and inhibited the expression of the components of NLRP3 inflammasome including caspase-1p20 (a functional caspase-1 subunit) and IL-1β in ankle joint synovial tissues of AIA rats. In addition, molecular docking revealed that this bioactive exhibited better binding affinity with the following targets Src, JAK2, MEK1, ERK2, JNK1, p38 MAPK, EGFR, and KDR, particularly p38MAPK by forming hydrogen bonds with Met109 and Gly110 at its hinge region and caspase-1 (one of the three components of NLRP3 inflammasome). These observations and other findings highlight the benefit of the plant containing these bioactive compounds in the treatment of RA.[196]

Tamarindus indica contains abundant bioactive compounds, including procyanidins, catechin, taxifolin, apigenin, luteolin, and naringenin, and preclinical evidence, showed that these phytoconstituents mediate anti-inflammatory activity *in vitro* and *in vivo*.[231] Other relevant bioactive compounds predominant in *T. indica* include 9,12-Octadecadienoic acid (Z, Z)-, *n*-Hexadecanoic acid, cis-Vaccenic acid, Benzene, 1-ethyl-2,3-dimethyl, beta-Sitosterol, gamma-Tocopherol, Octadecanoic acid, Benzene, 1,2,3-trimethyl-, and Spiro[3.5] nona-5,7-dien-1-one, 5,9,9-trimet.[232] Available information in the pharmacopeia reveals that crude extract of *T. indica* possesses antiarthritic function *in vivo. T. indica* seed crude extract (50 mg/kg) reversed paw swelling/volume and reduced pannus formation in CFA-induced arthritis rats. In addition, *T. indica* improves arthritic-induced cartilage degradation by decreasing the activities of serum hyaluronidase and MMPs, including MMP-2, -3, -9, and -13; ameliorates arthritic-induced bone degeneration by suppressing the activities of cathepsin K – a mammalian collagenase that is involved in the pathogenesis of several inflammatory disorders including RA, N-acetyl hexosaminidase, β-D-glucuronidase, cathepsin D, alkaline phosphatase (ALP), acid phosphatase (ACP), tartrate-resistant acid phosphatase (TRAP); mitigates arthritic-induced inflammatory mediators by retarding the levels of TNF-α, IL-1β, IL-6, IL-23, and COX-2 while increasing the level of IL-10 – an anti-inflammatory marker; abrogates arthritic-induced endogenous generation of ROS and hydroperoxides; sustains an intracellular level of GSH; and restores altered expression level of SOD, CAT, and GST. The observed antiarthritic effect could be due to anti-inflammatory bioactive compounds, including threo-Isocitric acid, galactosyl glycerol, procyanidin B2, arecatannin B1, catechin, rutin, and embelin.[197] The antiarthritic effect of these reported bioactive compounds, including rutin,[192–194] catechin,[198] and embelin,[199] is documented in the pharmacopeia.

Securidaca longipedunculata is a medicinal plant with known ethnomedicinal benefits. It is used in a traditional setting to treat hernias, coughs, ascariasis, constipation, headaches, rheumatism, stomach ache, malaria, tuberculosis, pain, epilepsy, pneumonia, skin infections, and increased sexual drives in men.[233] Bioactive compounds identified in different parts of *S. longipedunculata* include securidacaside A and securidacaside B (saponins),[234] 1,7-dihydroxy-4-methoxyxanthone and rutin (flavonoid),[235,236] β-sitosterol (steroid), sinapic acid, 4,5-dicaffeoyl-D-quinic acid, caffeic acid, 3,4,5-tricaffeoyl-D-quinic acid, Quercetin, *p*-coumaric acid, cinnamic acid, caffeic acid, and chlorogenic acid (phenolic acids).[235,237] There is no experimental and clinical evidence revealing the antiarthritic effect of the crude extract of the plant; however, some of the bioactive compounds found in the plant have antiarthritic activities. For instance, the antiarthritic effects of quercetin,[177–179] caffeic acid,[191] and chlorogenic acid[200,238] have been reported.

Piper guineense is a widely used spice and medicinal plant in Nigeria, especially among the Igbos. In Igbo cultural festivals, *P. guineense* is used as a spice to prepare "Gi

mmiri oku" (yam pepper soup), egusi, and oha soup. In an ethnomedicinal setting, many CAM adherents believe that the decoction of the leaves of the plant can protect against inflammatory disorders, diabetes, and other sundry diseases. Experimental evidence shows that *P. guineense* contains bioactive compounds, such as safrole, dillapiole, linalool, myristicin, β-caryophyllene, α-phellandrene, α-pinene, β-cymene, (E)-ocimene, piperine, and camphene.[239–241] To the best of our knowledge, no information pharmaceutically reveals the antiarthritic effect of *P. guineense.*

Further querying showed that some of the bioactive compounds' antiarthritic effects were some of the bioactive compounds had been investigated. For instance, 1-ppeperoyl piperidine (piperine), an alkaloid that is responsible for the plant's pungent smell, has been tested against arthritic models, including carrageenan-induced paw edema, croton pellet granuloma, and croton-induced granuloma pouch in male Albino rats of Hindustan Antibiotics (HA) and the results revealed that piperine (10 mg/kg) reduced significantly raw paw edema, the weight of cotton pellet granuloma, and croton-mediated granuloma pouch.[202] In another study, piperine (10–100 μg/mL) suppressed the expression of IL-6 and MMP-13, reduced the production of PGE2, nociceptive, and arthritic symptoms and inhibited the migration of activator protein (AP-1) into the nucleus of IL-1β-stimulated FLS in rats arthritic mode. The inti-arthritic activity of piperine was similar to that of Oxyphenylbutazone – a known standard drug for RAl.[242]

Leptadenia hastate is another ubiquitous medicinal plant used in Nigeria to stop bleeding and treat wounds. It is rich in bioactive compounds, including quinine, scopoletin, silibinin, dihydroxycoumarin, lupeol, lutein, β-carotene, cynanforidin, and gagminin.[243–245] The treatment of lupeol (42 mmol/ear) on the ear of male albino mice induced with croton prevented edema by 80%. Further structural modifications on lupeol, including acetylation, palmitoylation, and hemisuccinate ester, resulted in 72%, 54%, and 90% reduction in edema.[243] Previously, it was reported that lupeol (50 mg/kg) inhibited adjuvant-induced arthritis in rats by suppressing the activities of lysosomal enzymes, including β-glucuronidase, acid phosphatase, cathepsin D, and N-acetylglucosaminidase in the plasma, liver, kidney, and spleen; reduced the levels of plasma protein-bound carbohydrates including hexose, hexosamine, hexuronic acid, fucose, and sialic acid; and increased collagen urinary contents of hydroxyproline, hexosamine, hexuronic acid, and glycosaminoglycan.[204] These findings were further validated in other studies where 50 mg/kg of lupeol extracted from *Calotropis gigantea* reduced rat paw edema and decreased proinflammatory markers' expression (IL-1β, TNF-α, and IL-6) but maintained the level of IL-10 similar to the control and indomethacin groups.[246]

Piper nigrum has several ethnobotanical uses in Nigeria. Some used it as spice and seasoning during food preparation, while others used it to enhance digestion, facilitate weight loss, stimulate appetite, clear congestion, and manage arthritis. Several analytical techniques have been used to isolate and characterize the bioactive compounds present in *P. nigrum* and reported outcomes to show that the plant is rich in δ^3-carene, α-pinene, β-pinene, limonene, piperine, α-terpinen-4-ol, *p*-cymene, β-caryophyllene, β-phellandrene, α-phellandrene, α-thujene, sabinene, 5,3-carene, syvestrene, nerolidol, D-limonene, and β-bisabolene.[247] The anecdotal evidence that the fruit of *P. nigrum* can be used to treat and manage arthritis is yet to be validated experimentally. However, some of the identified bioactive compounds, especially piperine[202] and β-caryophyllene,[205,248] have been demonstrated to proffer antiarthritic functions. Therefore, an investigation into the anti-RA effect of crude and pure extracts of the plant is warranted.

Allium sativum is a common condiment used in Nigerian homes to prepare delicacies, including stew, various soups, and ethnomedicine to relieve high blood pressure, toothache, and other sundry medical applications. The bioactive compounds in *A. sativum* include alliin, allicin, (E)-ajoene, (Z)-ajoene, allylsulfide, 1,2-vinyldithiin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, and S-allyl-cysteine.[249,250] There are several preclinical and clinical evidence showing the antiarthritic effect of RA. In a randomized, double-blind, placebo-controlled trial study involving 70 women with RA divided into control (received placebo) and intervention (supplemented with 1000 mg of *A. sativum*) groups for 8 weeks, it was observed that *A. sativum* significantly decreased the serum levels of C-reactive protein (CRP) ($P = 0.018$) and TNF-a ($P < 0.001$), reduced pain intensity, tender joint count, disease activity score (DAS-28), and fatigue ($P < 0.001$; for all), and decreased swollen joint count ($P < 0.001$).[251] In another randomized, double-blind, placebo-controlled, parallel-design trial, 70 women were divided into two groups, receiving two tablets of either 500 mg *A. sativum* or placebo daily for 8 weeks. The results revealed that supplementation with *A. sativum* resulted in a significant increase in TAOC ($P = 0.026$), decreased MDA levels ($P = 0.032$), and reduced pain after activity ($P < 0.001$).[252] Diallyl disulfide (20 and 50 mg/kg), an active bioactive compound in *A. sativum*, protected against complete Freund's adjuvant (CFA)-induced arthritic in rats by significantly reducing paw volume, edema formation, arthritic score, and organ indices, improved joint destruction, and reduced inflammation.[253] In another study, diallyl disulfide inhibited paw edema, diminished serological CRP levels, and transcription of TNF-α, interleukin-1 beta (IL-1β), interleukin-2 (IL-2, Il2), inducible nitric oxide synthase (iNOS), nitric oxide (NO), COX-2, PGE_2, monocyte chemoattractant protein-1 (MCP-1), nuclear factor-kappa B (NF-κB), and myeloperoxidase (MPO) activity. In contrast, interleukin-10 (IL-10) and GSH levels were increased in the injured paw tissue of carrageenan-challenged rats.[206]

Cola nítida seed is mainly consumed by the elderly in different ethnic groups in Nigeria. It serves as the symbol of friendship, peace, and wishes for goodwill. It is an essential ingredient in most traditional ceremonies, such as yam festival, dowry rite, burial rite, and other sundry celebrations. Ethnomedicinally, the seed of *C. nitida* is a consumed stimulant to resist lethargy and to wake at night due to the high content of caffeine.[254] Industrially, *C. nitida* seeds serve as a raw material for producing certain drugs, drinks, beverages, wines, and candies.[255] Phytochemical quantification of methanol extract of *C. nitida* revealed the presence of alkaloids, anthraquinones, cardiac glycosides, flavonoids, steroids, tannins, and terpenoids.[256,257]

Further characterization of *C. nitida* reveals the presence of caffeine, d-catechin, L-epicatechin, theobromine, vitamin E, stigmasterol, diethyl phthalate, β,γ-sitosterol, and kolatin, among a host of other phytoconstituents.[258,259] Evaluation of the antiarthritic effect of *C. nitida* against carrageenan-induced paw edema in rats has been elucidated. Crude extract of *C. nitida* at 50, 100, and 200 mg/kg reduced rat paw edema similar to diclofenac (10 mg/kg).[256] The observed antiarthritic potential of crude extract of *C. nitida* in rats could be due to numerous antioxidants and phytochemicals that can scavenge ROS and RNS and avert the onset of RA in humans and animals.[260] The antiarthritic effect of stigmasterol, a known bioactive compound in *C. nitida*, has been investigated in the collagen-induced arthritic (CIA) model of arthritic. The results reveal that stigmasterol treatment improves clinical severity and histological alterations in CIA rats, reduces joint damage, restrains the increased articular elastase activity, and suppresses the expression of TNF-α, IL-6, IL-1β, iNOS, and COX-2 while upregulating the expression of IL-10 through the downregulation of NF-kBp65 and p38MAPK in joints.[207] Caffeine is the most active ingredient in *C. nitida* seeds. Current evidence reveals that a high intake of *C. nitida* and its binding to adenosine receptor A2a can significantly upturn the generation of interferon-gamma (IFN-γ) in $CD4^+$ T cells of peripheral blood mononuclear cells (PBMCs) collected from RA patients, therefore promoting inflammation and the burden of RA.[261] These findings call for further investigation to determine the effective dose of *C. nitida* that can be of therapeutic significance to patients diagnosed with RA or sensitize the populace to the danger of *C. nitida* seed ingestion by patients with RA.

Vernonia amygdalina is a vegetable widely cultivated among the Ibos and some ethnic nationalities in Nigeria. It is a significant vegetable for preparing Igbo native soup called "ofu onuigbo" and can serve as spice and seasoning to prepare porridge yam and plantain. Ethnomedicinally, an aqueous extract of *V. amygdalina* can be used to treat and manage gastrointestinal disorders, diabetes, malaria, and a host of other diseases.[262] *V. amygdalina* contains abundant phytochemicals, including flavonoids, terpenoids, alkaloids, tannins, saponins, glycosides, steroids, and phenols. Characterization of the bioactive compounds in *V. amygdalina* using spectral analytical techniques reveals the following compounds: vernolide, vernodalol, hexadecanoic acid ethyl ester, 1,1-diethoxy-3-methyl butane, phytol, β-Sitosterol, squalene, linoleic acid ethyl ester, caffeoylquinic acids, flavanone-O-rutinoside, luteolin, apigenin derivative, and vernonioside D.[208,263,264] The antiarthritic effect of *V. amygdalina* crude extract has been evaluated. The extract at 300 mg/kg markedly downregulates the expression of PGE2, NF-κβ, IL-1β, ADAMTS-5, collagen type 10α1, and caspase3; reduces serum collagenases (MMP-3 and MMP-13) and collagen type II degradation biomarker (CTX-II) levels; and upregulates the anti-inflammatory IL-10 and collagen type 2α1 mRNA expressions in monosodium iodoacetate-induced arthritis model in ovariectomized female rats.[208] Luteolin, one of the bioactive compounds in *V. amygdalina*, has proffered an antiarthritic effect in IL-1β-induced FLS of RSC-364 cells. Luteolin was demonstrated to significantly decrease the expression of critical molecules in NF-κB and JAK/STAT-signaling pathways, including NF-κB p50, p100, IKKα/β, gp103, JAK1, STAT3, phospho-IKKα/β, and phospho-STAT3.[265]

Ocimum gratissimum is used as spice and seasoning to prepare pepper soup, egusi soup, and other Nigerian delicacies. Folklorically, the extract of *O. gratissimum* is used to treat various ailments, including diarrhea, fever, conjunctivitis, pneumonia, dermatitis, cough, and malaria.[266] Quantitative phytochemical screening of *O. gratissimum* reveals the following secondary metabolites: alkaloids, saponins, tannins, phlobatannins, glycosides, phenols, and anthraquinones.[267] Chemical profiling of the leaf extracts of *O. gratissimum* by GC–MS reveals the following bioactive compounds: sabinene, γ-terpene, thymol, α-copaene, trans-caryophyllene, α-humulene, β-selinene, caryophyllene oxide, trans-phytol, cymene, N-acetylproline, neophytadiene, β-bisabolene, germacrene D, α-farnese, eugenol, camphor, and β-pinene.[268,269] There are folkloric claims that the extracts of *O. occiumum* proffer antiarthritic functions. To validate this, treatment with 500 mg/kg of 95% ethanolic extract of *O. gratissimum* nullified CIA in female Sprague-Dawley rats by decreasing paw volume, lowering arthritic scores and suppressing the expression of TNF-α in CIA rats. The antiarthritic effect of one of the individual bioactive compounds in *O. gratissimum* has been evaluated *in vivo*. In a carrageenan-induced arthritis rat model, eugenol at 2.50, 5.0, or 10 mg/kg significantly decreased inflammatory cells' infiltration, suppressed the arginase adenosine triphosphate activities, and adenosine monophosphate hydrolyse, and increased adenosine diphosphate hydrolysis and adenosine deaminase activities dose-dependently.[188] Since more of these bioactive compounds mediate antioxidative effects, more *in vitro* and *in vivo* studies are warranted to properly elucidate these compounds' anti-inflammatory and antiarthritic effects and validate the folkloric claims that *O. gratissimum* is a potent medicinal plant for the treatment and management of RA.

Solanum melongena is a ubiquitous plant in Nigeria. It brings forth an edible fruit widely consumed fresh by Nigerians as desserts, especially during ceremonies. The fruits of *S. melongena* and seeds of *C. nitida* are symbolic in the culture of the Ibos, Yoruba, and some other ethnic groups in Nigeria. Many traditionalists commonly distribute the plant products to dignitaries during the burial, traditional marriage, name giving, and new yam festivals. CAM practitioners in Nigeria believe that the consumption of *S. melongena* fruits can prevent inflammatory disorders, serve as purgative to ease urination, and stimulate sex drive (hence the frequent use of the fruits among newly married couples). Several bioactive compounds have been identified in *S. melongena*, including solasodine, solasonine, solamargine,[270] kaempferol, quercetin, apigenin, isorhamnetin,[271] chlorogenic acid, caffeoylquinic acid,[272] nasunin,[273] and carotenoids, such as lutein and zeaxanthin.[274] Apigenin, one of the bioactive compounds in *S. melongena*, confers a protective effect against RA. In a CIA mouse, the administration of apigenin reduces joint swelling, the expression of TNF-α, IL-1β, and IL-6 in CIA mice, DC maturation during the acute phase, expression of CXCR4 on peripheral blood, and the percentage of DCs in LNs and changes in DC subset of LNs.[209]

Capsicum annuum is another important plant-based condiment commonly used to prepare all Nigerian delicacies.

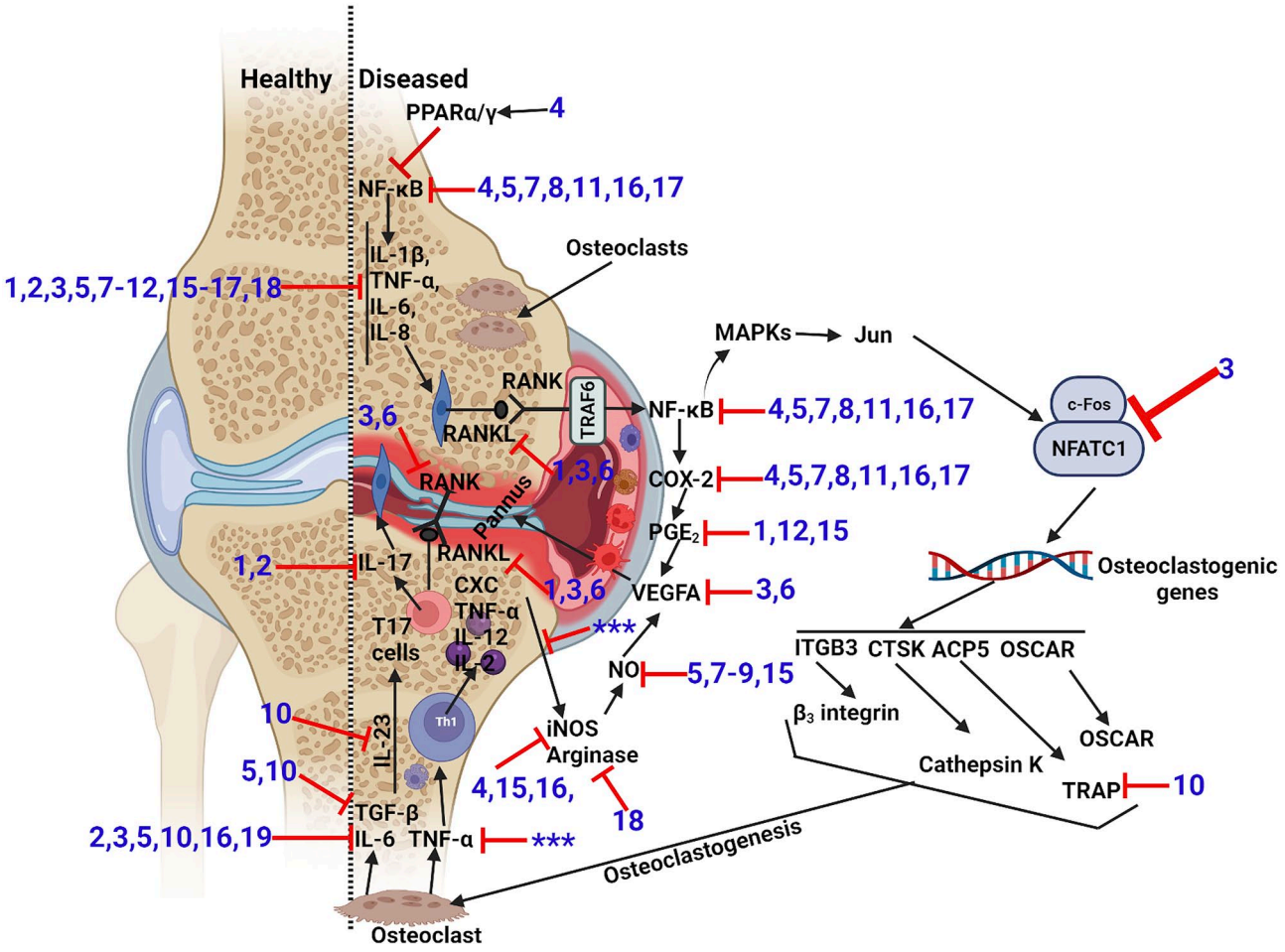

Figure 10. Schematics showing health and RA joints and possible targets of inhibition by different bioactive compounds in the included medicinal plants. (A color version of this figure is available in the online journal.)
The scheme was modeled with Bioredender.com by Arunsi U.O.
1–19: Bioactive compounds in medicinal plants listed in Table 1; PPARα/γ: Peroxisome proliferator-activated receptor alpha or gamma; TRAF6: TNF receptor-associated factor 6; NF-κB: Nuclear factor-kappa B; IL-1β: Interleukin 1-beta; TNF-α: Tumor necrosis factor-alpha; IL-6: Interleukin 6; IL-8: Interleukin 8; IL-17: Interleukin 17; Il-23: Interleukin 23; TGF-β: Transforming growth factor-beta; RANKL: receptor activator of nuclear factor-κB ligand; RANK: receptor activator of nuclear factor-κB receptor; CXC: Chemokines; iNOS: Inducible nitric oxide synthase; NO: Nitric oxide; VEGFA: Vascular endothelial growth factor ligand A; PGE_2: Prostaglandin E_2; COX-2: Cyclooxygenase 2; MAPK: Mitogen-activated protein kinase; NFATC1: Nuclear factor of activated T cells 1; OSCAR: Osteoclast associated immunoglobulin-like receptor; TRAP: Tartrate-resistant acid phosphatase.

The seeds of *C. annuum* can be eaten fresh or dried, blended and roasted in fish and meat. There are folkloric claims that this plant is used to treat stomach ulcers, wounds, toothache, sore throat, and parasitic infections. These beliefs stem from the preponderance of bioactive compounds present in the plants, including capsaicin, dihydrocapsaicin,[275] beta-carotene, beta-cryptoxanthin, zeaxanthin, polyphenols, and proanthocyanidins.[276] Capsaicin, one of the most active bioactive compounds, has been demonstrated to inhibit collagenase expression from synoviocytes and suppress the synthesis of PGE_2.[210]

Bioactive compounds as possible therapeutic targets for RA

Studies in pharmacopeia revealed that bioactive compounds present in plant botanicals possess an anti-RA effect by blocking several signaling nodes leading to the suppression of the activation and differentiation of proinflammatory cells and generating soluble molecules known to trigger RA pathogenesis in the synoviocytes (Figure 10). In a healthy joint, the activation of some signaling networks and the expression of inflammatory cells and molecules are under stringent control. However, signaling networks are switched on in diseased joints, causing the expression of proinflammatory cytokines and chemokines, such as IL-1β, TNF-α, IL-6, IL-8, and IL-17. The accumulations of these molecules then trigger the expression of RANK on osteoblasts and the synthesis of RANKL by inflammatory cells and synovial fibroblasts.[176,189] RANKL binds to RANK and activates TRAF6; activated TRAF6 stimulates the nuclear translocation of NF-κB. This transcription factor regulates several processes in the development of RA. Precisely, NF-κB activates MAPK, which drives the activation of Jun.

Jun mediates the dimerization of c-fos and NFATC1, leading to the upregulation in the expression of osteoclastogenic genes, including ITGB3, CTSK, ACP5, and OSCAR. The expression of these genes is important for the synthesis of β3-integrin, cathepsin K, TRAP, and OSCAR, which are known to activate osteoclasts in the synoviocytes, leading

to bone and cartilage destruction.[180,277] Activated osteoclasts express soluble proteins, such as IL-6, TNF-α, and TGF-β, needed to expand the population of inflammatory T cells, including T1 cells, T17 cells. Other inflammatory innate cells, such as mast cells, neutrophils, and dendritic cells – known to increase the severity of RA[277,278] are also included. The expansion and degranulation of these cells result in the production of more soluble proteins necessary for the expression of RANKL/RANK on different cells in the synovium membrane. In addition, the expression of arginase and iNOS by these cells drives RA via NO production. NO mediates the expression of proangiogenic factors, such as VEGF and VEGFR.[189] The interaction of VEGF and VEGFR on the different proinflammatory cells and synovial fibroblasts drives angiogenesis – a hallmark of RA. NF-κB activation can also cause the pathogenesis of RA via the expression of COX-2. COX-2 acts on arachidonic acid in the prostaglandin pathway and produces PGE_2. This molecule, in turn, increases the expression of VEGF/VEGFR – leading to angiogenesis in the synovial membrane. NF-κB, on activation, can exit into the nucleus, where it activates several gene-encoding inflammatory cytokines, chemokines, MMPs (MMP-2, -3, -9, -13), and other soluble proteins that orchestrate RA.[197,198,242]

Studies using advanced chromatographic techniques, including GC–MS, high-performance liquid chromatography (HPLC), Fourier-transformed infrared (FT-IR), high-resolution mass spectrometry (HR-MS), and nuclear magnetic resonance (NMR), has improved our understanding on the novel role of medicinal plants in the treatment of RA. Plant-based bioactive compounds have been shown to modulate signaling pathways in RA effectively and might serve as potential inhibitors for the design of drugs against RA. Furthermore, as can be seen in Figure 8, bioactive compounds, such as citral or geranial, can drive the upregulation of PPARα/γ expression in the synoviocytes and inhibit NF-κB activation and its translocation into the nucleus; eugenol, caffeic acid, rutin, chlorogenic acid, stigmasterol, and caffeoylquinic acid target NF-κB pathway and inhibit its activation and translocation into the nucleus and mediate the downstream inhibition of the expression of COX-2; 6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol, piperine, and diallyl sulfide can act on COX-2 and suppress the generation of PGE_2; curcumin and apigenin can inhibit the expression of angiogenic factors including VEGF A and VEGFR; eugenol, caffeic acid, rutin, α-pinene, β-caryophyllene, and diallyl sulfides can act synergistically to inhibit the production of NO; the combination of geranials, diallyl sulfide, and stigmasterol can inhibit the expression of iNOS and the production of NO, and eugenol can inhibit the expression of arginase and the eventual production of NO; 6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol, quercetin, eugenol, caffeic acid, rutin, α-pinene, β-caryophyllene, threo-Isocitric acid, galactosyl glycerol, procyanidin B2, arecatannin B1, catechin, embelin, chlorogenic acid, piperine, diallyl sulfides, stigmasterol, caffeoylquinic acid, and eugenol can inhibit the production of proinflammatory cytokines and chemokines and modulate the expansion of proinflammatory immune cells such as mast cells, neutrophils, monocytes, macrophages, dendritic cells, NK cells, and T cell lineages (especially Th1 cells and T17 cells); curcumin and apigenin can effectively inhibit the expression of RANK/RANKL, 6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol and quercetin can suppress the production of IL-17 by T17 cells thereby suppressing inflammation in the synoviocytes; eugenols, threo-Isocitric acid, galactosyl glycerol, procyanidin B2, arecatannin B1, catechin, and embelin can decrease the expression of IL-6, TGF-β, and IL-23 needed to facilitate the polarization of $CD4^+$ T cells into T17 cells, curcumin can inhibit the dimerization of c-FOS and NFATC1; while threo-Isocitric acid, galactosyl glycerol, procyanidin B2, arecatannin B1, catechin, and embelin can synergistically inhibit the expression of TRAP, leading to the inhibition of osteoclastogenesis in diseased joints. The appropriate combination of these phytoconstituents in the right proportion can change the course of targeting RA in the clinics and may open new inroads in drug discovery and therapeutics.

Repurposing of herbal remedies for effective treatment of RA

Repurposing or reprofiling will be an alternative strategy to increase the therapeutic index and safety margin of novel plant-based regimens in the effective management of RA. The biochemicals found in herbal remedies act on different targets, including cl, sf, and ip, to suppress arthritic scores and clinical features. It is necessary to repurpose these bioactive compounds based on established mechanisms of action and combine medicinal plants and bioactive compounds that target important signaling nodes involved in the pathogenesis of RA. Proper knowledge of the bioactive compounds' composition in these medicinal plants using advanced techniques would improve the way experimentalists target RA in a preclinical setting. For instance, the combination of medicinal plants that target PPARα/γ, NF-κB, IL-1β, TNF-α, IL-6, IL-8, CXC, RANK/RANKL, VEGFR/VEGF, iNOS, arginase, COX-2, PGE2, c-FOS, NFACT1, and TRAP (Table 3) will be a novel model for developing accessible anti-RA therapy that is tolerable. The treatment contains biochemicals that can effectively target significant pathways involved in the development of RA or serve as a detoxifier to reduce the side effects of conventional drugs use in RA patients.

We have demonstrated the potential benefits of bioactive compounds derived from medicinal plants. However, it is pertinent to address emerging issues raised by clinicians on the safety of CAM as an alternative to conventional therapies used in the treatment of RA. Many have asked how effective and safe is CAM and how can it be administered to patients? Nonetheless, few randomized clinical trials (RCTs) delineate the efficacy and safety of some of these bioactive compounds as a potent therapy for treating patients with active RA (Table 4). These studies validate the use of plant-based treatment to treat patients with active RA and intend to rouse the attention of ethnomedicinal professionals in conducting more RCTs using different bioactive compounds from plants with known anti-RA activity. The effective screening of indigenous medicinal plants and herbs to identify bioactive compounds that can target intracellular signaling pathways and inhibit the generation of proinflammatory factors known to promote RA would reduce the burden of RA globally and increase the therapeutic targets of plant-based therapies.

Table 3. Medicinal plants reprofiling/repurposing in RA treatment.

S/N	Therapeutic targets	Potential medicinal plants
1	↑PPARα/γ	*C. citratus*
2	↓NF-κB	*C. citratus, S. aromaticum, N. latifolia, O. basilicum, S. longepedunculata, C. nitida, V. amygdalina*
3	↓IL-1β, TNF-α, IL-16, IL-8, CXC	*Z. officinale, A. cepa, C. longa, C. articulatus, T. indica, P. guineense, A. sativum, O. gratissimum*
4	↓RANK/RANKL	*C. occidentalis, Z. officinale, A. cepa*
5	↓VEGF/VEGFR	*C. longa, C. occidentalis*
6	↓iNOS, arginase, COX-2, PGE_2	*C. citratus, A. sativum, C. nitida*
7.	↓c-FOS, NFATC1, TRAP	*C. longa, N. latifolia*,

PPARα/γ: Peroxisome proliferator-activated receptor alpha or gamma; NF-κB: Nuclear factor-kappa B; IL-1β: Interleukin 1-beta; TNF-α: Tumor necrosis factor-alpha; IL-16: Interleukin 16; IL-8: Interleukin 8; CXC: Chemokines; RANK: receptor activator of nuclear factor-κB receptor; RANKL: receptor activator of nuclear factor-κB ligand; iNOS: Inducible nitric oxide synthase; COX-2: Cyclooxygenase 2; NFATC1: Nuclear factor of activated T cells 1; TRAP: Tartrate resistant acid phosphatase.
↑: Upregulation; ↓: Downregulation.

Table 4. Summary of randomized clinical trials included in the mini-review.

References	Bioactive compounds	Design	Subjects	Treatments	Main results
[279]	Curcumin	Randomized, single-blinded, pilot study	45 patients with active RA meeting ACR criteria for at least 8 weeks. Mean ages in cohort groups: 47.8 years in curcumin cohort, 47 years in curcumin + diclofenac cohort, and 48.87 years in diclofenac cohort.	500 mg curcumin (Group 1), or 500 mg curcumin + 50 mg diclofenac sodium (Group II), or 50 mg diclofenac sodium.	Groups I, II, and III after 8 weeks showed significant changes in DAS score, with curcumin (Group I) exhibiting the highest percentage improvement in overall DAS and ACR scores (ACR 20, 50, and 70), and these scores were significantly better than patients in Group III ($P < 0.05$). In addition, curcumin group did not manifest any adverse events.
[280]	Ginger	Randomized, double-blind, placebo-controlled clinical trial	70 active RA patients meeting ACR criteria for at least 2 years of disease duration, being under treatment with DMARDs: methotrexate, hydroxychloroquine, and prednisolone < 10 mg/day) and not receiving NSAIDs as far as possible, aged 19–69 years.	1500 mg/day of ginger powder (Group I) or placebo, fried wheat powder that had served 2 weeks in ginger powder box for getting ginger smell (Group II) for 12 weeks.	Group I versus Group II, after 2 weeks, improved the expression of Foxp3 ($P = 0.02$), and PPAR-γ ($P = 0.047$) within the ginger group while significantly decreasing the expression of Tbet and RORγt ($P < 0.05$); however, the difference within the group was not statistically significant ($P = 0.12$). In addition, reduction in DAS score was statistically significant in ginger group and between the two groups after intervention ($P = 0.003$).
[281]	Ginger	Randomized, double-blind, placebo-controlled clinical trial	66 active RA patients meeting ACR criteria with 2 years disease duration during 2013–2016, aged 19–69 years.	1500 mg/day of ginger powder (Group I) or placebo, fried wheat powder that had served 2 weeks in ginger powder box for getting ginger smell (Group II) for 12 weeks.	Ginger powder supplementation significantly decreased CRP ($P = 0.05$) and the expression of L-1β mRNA level ($P = 0.021$), and non-statically decrease the expression of TNF mRNA level ($P = 0.093$).
[282]	Quercetin	Randomized, double-blind, placebo-controlled clinical trial	50 women with RA who met the ACR criteria and were suffering from chronic diseases (including acute heart, kidney, and liver diseases), not taking any antioxidant supplements, did not change the type and dose of medications at least 1 month prior to the study and were not smokers, aged 19–70 years.	500 mg/day quercetin capsule (group I) or placebo, containing lactose capsule (group II) for 8 weeks.	Quercetin supplementation for 8 weeks significantly reduced EMS, morning pain, and after activity pain ($P < 0.05$), decreased DAS-28 and HAQ scores compared to the placebo, and the number of patients with active disease significantly decreased in the quercetin group. In addition, plasma level of hs-TNF-α significantly reduced in the quercetin group compared to the placebo ($P < 0.05$).

RA: Rheumatoid arthritis; Hs-TNF-α: High-sensitivity tumor necrosis factor; DAS: disease activity score; HAQ: Health Assessment Questionnaire; CRP: C-reactive protein; ACR: American College of Rheumatology.

Conclusions

This mini-review highlights the role of bioactive compounds derived from medicinal plants in treating and managing RA and a novel combination model to increase anti-RA therapies' efficacy and therapeutic index of traditional medicine. This mini-review highlights the bioactive compounds in medicinal plants, suppressing signaling nodes orchestrating RA development. Factors that also reduce proinflammatory cues and suppress oxidative stress and nitrosative stress in RA

patients and arthritic animal models are also addressed – at the same time, providing a safe mechanism for resolving inflammation and increasing antioxidant buffering capacity.

Therefore, we recommend that a proper mixture of these bioactive compounds identified in preclinical studies using different arthritic models may open novel therapeutic windows for the treatment and management of RA in Nigeria, and the combination of most of these natural products with some conventional drugs, such as methotrexate, may increase their safety margin. In the findings of Banji *et al.*,[283] curcumin (30 and 100 mg/kg) combined with a subtherapeutic dose of methotrexate (1 mg/kg) salvaged hepatotoxicity, oxidative stress, and FCA-induced arthritis in rats. Animals treated with methotrexate alone exhibited high aminotransferase, alkaline phosphatase, total and direct bilirubin, and lipid peroxides levels. This finding suggests that the concomitant administration of curcumin with methotrexate could synergistically increase the safety margin of methotrexate.

In Nigeria, to the best of our knowledge, there is no RCT data to validate the clinical basis of these bioactive compounds in the management of patients diagnosed with RA. We are unsure if these medicinal plants and herbs could replace conventional therapies for RA treatment. But RCT evidence has shown that some of the included bioactive compounds are more effective and safer for treating RA than conventional therapy. Therefore, the mini-review warrants extensive research to validate CAM use in treating RA and other debilitating diseases. Validation of CAM applications in regions where CAM use policy has been poorly enacted or disprove CAM practice if the observed anecdotal and experimental claims are false. CAM practice in Nigeria is already going into extinction due to diminished ethnomedicinal research, experimental validation, and revalidation of folklore knowledge of the medicinal plant. Underlying this apathy is limited funding for preclinical studies to probe the anti-RA effect, a dearth of RCTs of bioactive compounds with acclaimed healing effects, and sanctions imposed on CAM practice following petitions by the Medical and Dental Council of Nigeria (MDCN) and the Pharmacists Council of Nigeria (PCN). However, if these issues are addressed through pragmatic RCTs, CAM practice in Nigeria would rouse the hope of patients with active RA and other broad-spectrum disabilities that plague humankind.

AUTHORS' CONTRIBUTIONS

U.O.A. and S.E.O. performed an initial search and designed the model for targeting signaling networks in rheumatoid arthritis; O.E.C. and P.E.E. performed an ethnobotanical search on the geographical distribution and utilization of Nigerian indigenous plants; U.O.A. and S.E.O. were involved in the review of the content, revision of the text, and approval of the final article.

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