The Bioregulatory Approach to Work-related Musculoskeletal Disorders: Using the Multicomponent Ultra low–dose Medication Traumeel to Target the Multiple Pathophysiological Processes of the Disease

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The burden of chronic diseases in modern society is well recognized. Increasing resistance to existing drugs, a decreasing number of new effective drugs, and a growing number of comorbidities in the aging population force the medical community to look for innovative approaches in disease management. Bioregulatory medicine is one of such approaches. The multifactorial origin of many chronic diseases suggests multiple targets to be addressed when successful treatment is the goal. This also applies to most diseases with immunological and inflammatory pathophysiological features, such as work-related musculoskeletal disorders. Consequently, strategies for the development of either rationally designed multitargeted agents or the optimization of combining existing targeted agents are essential. Traumeel is a medication with bioregulatory properties that has been successfully applied to treat musculoskeletal injuries. This article provides an overview of current scientific evidence about this medication and proposes a hypothesis of possible mechanisms of action presented from a viewpoint of a pathophysiological model of work-related musculoskeletal disorders. (*Altern Ther Health Med.* 2011;17(2 Suppl):S8-S17.)

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Bioregulation is defined as the regulation of biological processes.[1] Bioregulatory medicine aims to target these processes in the human organism to restore proper functioning of autoregulating feedback loops that have been impaired during disease evolution. The hallmarks of bioregulatory medicine can be summarized in three ways: (1) a systems approach, which is used in clinical practice; (2) multitargeting features of the therapeutic method and preparations (the stage of the disease process is also considered); and (3) the ultra low–dose design of these preparations, which evokes multiple responses to a multitude of near-threshold stimuli produced by ultra low–diluted substances.

Multitargeted therapy becomes more and more the common buzzword in the medical and scientific community in light of increasing knowledge about the multifaceted nature of many diseases, especially chronic ones: increasing resistance to existing drugs, a decreasing number of new effective drugs, and a growing number of comorbidities in the aging population.[2,3] Targeting multiple pathways to reach optimal therapy has been favored when treating pneumonia,[4] dyslipidemia,[5] metabolic syndrome,[6] and many other diseases. Methodological approaches to multitargeted therapy in conventional medicine vary from combining several drugs[7,8] or natural compounds,[9] which are expected to exert synergistic effects, to designing new drug entities by nanotechnologies[10] or genetic engineering.[11] However, although multitargeting can be seen as a relatively new trend in therapeutic approaches in modern conventional medicine,[12] traditional medical approaches, such as traditional Chinese medicine,[13] traditional phytotherapy,[14] and other holistic therapy concepts, have applied multitargeting in their practice since their creation.

During the past few decades, knowledge about the ingenious complexity of human organisms, along with the complexity of common diseases and pathogenetic networks interrelating and connecting different organism systems, has been increasing. The image of a human being as an open and adaptive system that pursues the objectives of adaptation to the environment and survival has been repeatedly reinforced in the medical and scientific community.[15,16] Chapman et al,[15] in their perspective article, define "system" as a set of components constituting a whole within which a component interacts with or is related to at least one other component; ultimately, all components serve a common objective. Kaizu et al[17] emphasize that robustness against wide fluctuations (other than biological oscillations) in variables is considered a common design principle of a biological system. The view of such systems on the biology of the human organism has huge implications for medical thought because it encourages the medical community to sway more and more from a paradigm of treating major disorders and symptoms of the patient toward treating the patient as a whole unique system. Also, the system in this case possesses multiple options for responding to external interventions and displays a determination to sustain its own

activities.[18] The capability of the human organism to self-regulate to maintain homeostasis in a constantly changing external and internal environment via complex networks of feedback loops is a proposed target of many complementary medical systems, including traditional Chinese medicine,[19] acupuncture,[20] and bioregulatory medicine.[1]

One of such complex networks is an inflammatory network consisting of many inflammation-related components and their feedback loops, including cytokines, transcription factors, and regulatory genes.[21-23] This network plays a major role in the pathophysiological features of work-related musculoskeletal disorders (MSDs). For example, Xu and Murrell,[24] in their hypothesis of the pathogenesis of tendinopathy, suggest a model of interrelations between different functional networks, such as oxidative stress, apoptosis, matrix remodeling, tissue regeneration, and angiogenesis. It is well accepted that components of these functional networks are also regarded as players in inflammation-related processes. For example, reactive oxygen species may be essential secondary messengers signaling NLRP3/NALP3 (NOD-like receptor family, pyrin domain containing 3/NACHT, LRR, and PYD domains containing protein 3) inflammasome activation[25] or glucocorticoid receptors, which are implicated in programmed cell death, may change nuclear factor κB–dependent transcription.[26] The role of the inflammatory network in the pathophysiological features of work-related MSDs is well described by Barbe and Barr.[27]

Current pharmacological treatment approaches of MSDs are directed toward suppression of proinflammatory players of the previously mentioned network and involve the use of conventional antiinflammatory agents, such as steroids or nonsteroidal antiinflammatory drugs.[28] On the other hand, bioregulatory medications, such as Traumeel, are aimed at the modulation of both proinflammatory and antiinflammatory pathways vs suppression (Figure 1).

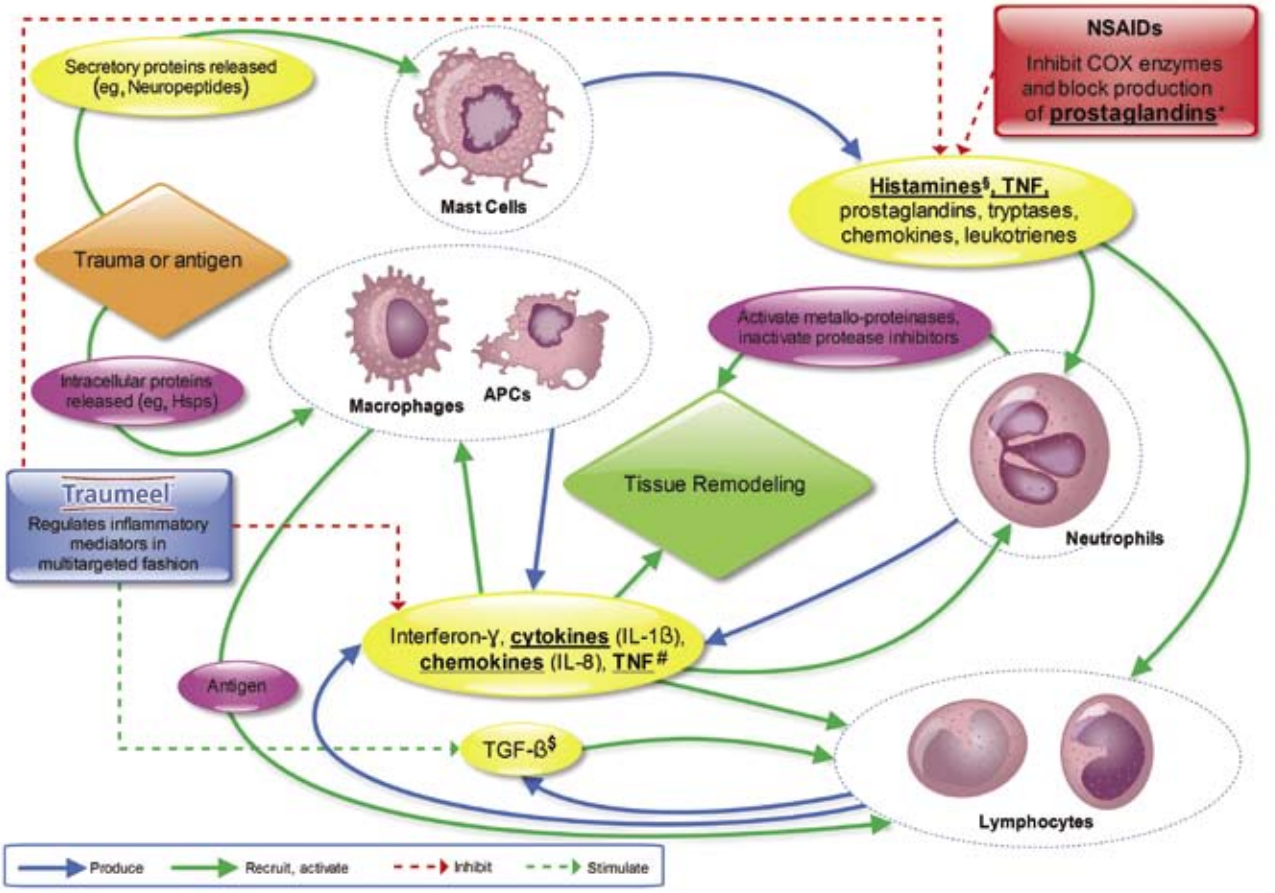

FIGURE 1 Role of Traumeel in the Inflammation Cascade (Adapted From Nathan[23])

Each cell commits to recruiting and activating other cells based on multiple inputs, generally requiring evidence of both injury and infection (not shown) before it joins fully in amplifying the inflammatory process. Interactions among leukocytes, endothelium, platelets, and coagulation factors; the generation of stop signals; and the flow of information over subsequent days, including the transition to wound healing, are not shown. *The inhibition of prostaglandins by nonsteroidal antiinflammatory drugs is not specified. §Data are taken from Baldwin and Bell.[58] #Data are taken from Porozov et al.[52] $Data are taken from Heine and Schmolz.[85] APCs indicates antigen presenting cells; COX, cyclooxygenase; Hsps, heat-shock proteins; IL, interleukin; NSAIDs, nonsteroidal antiinflammatory drugs; TGF, transforming growth factor; TNF, tumor necrosis factor.

This is achieved by including into a formula several components of natural origin in microdoses and ultra low doses that purportedly act synergistically in a multitargeted manner on various players of the inflammation network. As previously shown, many substances of various origins have biological activities in dose ranges from 10^{-2} to 10^{-24} or even higher dilution. Examples include the neuroprotective effects of ultra low–dose glutamate,[29,30] the inhibition of opioid-induced hyperalgesia by ultra low–dose naltrexone,[31] the inhibition of proinflammatory cytokines and the reversal of the downregulation of L-glutamate transporters by ultra low–dose naloxone,[32] the antigenotoxic effects of homeopathic cadmium,[33] liver protection by ultra low–dose *Chelidonium majus*,[34] the inhibition of angiogenesis by paclitaxel at ultra low concentrations,[35] the improvement of memory by ultra low doses of antibodies to S-100B antigen,[36] and the cytotoxic effects to adenocarcinoma cells of ultra diluted *Carcinosin*, *Phytolacca*, *Conium*, and *Thuja*.[37] The clinical application of medications designed in ultra low doses is still debatable. In studies with peanut-allergic subjects, long-term desensitization was achieved by treatment with microdoses of peanut protein. Researchers hypothesized that allergen injection immunotherapy acts through downregulation of allergen-specific T-helper cell 2 responses, increased T-helper cell 1 responses, or the induction of T-regulatory cells; they found increased levels of T-regulatory cells and interleukin (IL) 10 in patient serum samples.[38] Manipulating immunological responses (eg, T-regulatory cells[39]) seems to be one of the possible ways to use microdoses or ultra low doses for therapeutic applications. Some researchers suggest that ultra diluted substances, through a so-called immunological bystander reaction, might be able to regulate the immune component of a disease.[40] Traumeel is usually used to treat disorders associated with acute inflammatory conditions of the musculoskeletal system (better know as MSDs), such as ankle sprains,[41] work-related tendinopathies,[42] muscle strains,[43] and short-term injuries.[44]

As the US National Research Council and the Institute of Medicine describe, MSDs involving the upper extremities, the lower extremities, and the back are an important national health problem.[45] In their publication, they state that MSDs are one of the leading categories of injuries and illnesses in the workplace, resulting in high levels of pain, discomfort, lost work time, and disability[45]; therefore, a need for further research was clearly defined. Several research groups suggested pathophysiological models of MSDs, either as a specific indication (eg, tendinopathy[24]) or in perspective of systems biology.[27]

This article discusses how the evidence from preclinical studies with Traumeel fits with current pathophysiological models of work-related MSDs. The aim is to provide a view on the assumptions of possible mechanisms of action of Traumeel as a multicomponent and multitargeted medication.

REVIEW OF EVIDENCE FROM PRECLINICAL RESEARCH

Model of Work-related Muscoloskeletal Disorders and Proposed Contribution of Traumeel on Tissue Injury and Inflammation

To build a modeled overview of possible contributions of Traumeel to the pathophysiological features of MSDs, the pathophysiological model of work-related MSDs, suggested by Mary F. Barbe, PhD, and Ann E. Barr, PhD,[27] was adopted in this publication. Their model is drawn based on extensive reviews of available evidence[46,47] and supported by their work with experimental rat models.[48] This model provides a comprehensive overview of work-related MSDs and can give insights into a potential therapeutic intervention with multitargeted therapies and/or medications.

The researchers suggest that inflammation plays a central role in MSDs related to overuse injuries. Also, physiological inflammation is required to repair damaged tissue.[49] Balanced cytokine release is postulated to be a key to tissue recovery[50]; therefore, acute inflammation (if not too robust) is beneficial, whereas chronic inflammation is detrimental.[51]

Per the model, primary tissue damage causes cellular release of cytokines (ie, mediators of inflammation, cell proliferation, cell migration, and regeneration). Peripheral tissue cell types (eg, fibroblasts, myocytes, and endothelial cells) respond to damage by upregulating several proinflammatory proteins; these proteins include IL-1, IL-6, tumor necrosis factor (TNF) α, and prostaglandin E_2. Cytokines can also be released by other cell types (eg, dendritic and mast cells, neurons, and Schwann cells); those released during acute inflammation (eg, IL-1α, IL-1β, and TNF-α) mediate the proliferation and maturation of macrophages, other mononuclear cells, and fibroblasts. Then, activated macrophages and other mononuclear cells produce even more cytokines (eg, IL-1, IL-6, and IL-11), further stimulating inflammation (Barbe and Barr[27] reviewed this topic). Traumeel inhibits the secretion of proinflammatory cytokines (ie, IL-1β, IL-8, and TNF-α) in resting and activated (mobile) immune cells and (resident) gut epithelial cells in vitro[52] (Figure 2). Local treatment with Traumeel was also associated with a significant decrease of systemic IL-6 levels.[53] Traumeel may target epithelial and/or endothelial cells, macrophages, and T cells and inhibit cytokine production. These effects might be responsible for fever reduction, the inhibition of such cellular behavior as T-cell and macrophage activation, T- and B-cell growth and differentiation, neutrophil migration, endothelium activation, and permeability.[54] IL-1 enhances the expression of cyclooxygenase-2, which is involved in the synthesis of prostanoids (eg, prostaglandin E_2). IL-1 and TNF-α also serve as potent stimulators of osteoclast activity. According to Barr and Barbe, the "phagocytic action of the activated inflammatory cells and osteoclasts can result in direct tissue damage."[46] This leads to the initiation of chronic inflammation.[46] Although Traumeel is capable of stimulating phagocytosis and cell proliferation,[55] it also inhibits the IL-1 and TNF-α pathways. This multitargeted action prevents the vicious circle of reinforced tissue damage from activated inflammatory cells; rather, it modulates these cells toward tissue repair. The immunomodulating and beneficial phagocytosis-stimulating properties of Traumeel were supported by human research in patients with inflammatory periodontal disease and chronic generalized periodontitis.[56,57] In addition to epithelial cells and leukocytes, mast cells may be another important cellular target of

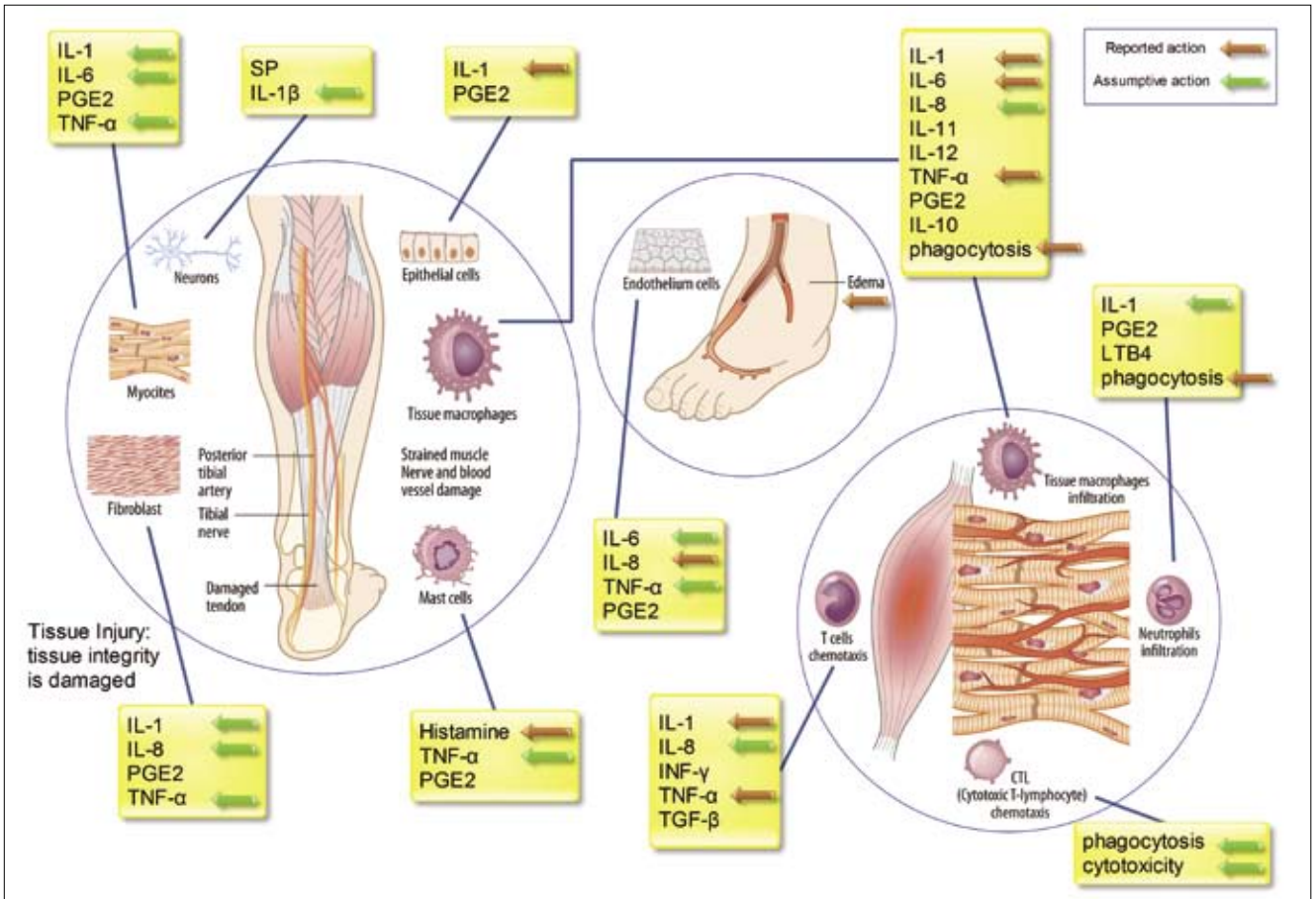

FIGURE 2 Reported (orange) and Assumptive (light green) Targets for Traumeel's Action in Inflammation

Traumeel acts on multiple cellular targets during tissue injury and local acute inflammation. These targets include tissue and blood macrophages, T lymphocytes, neutrophils, mast cells, and epithelial cells. The "Model of Work-related Musculoskeletal Disorders and Proposed Contribution of Traumeel on Tissue Injury and Inflammation" subsection of the "Review of Evidence From Preclinical Research" section provides explanations. IL indicates interleukin; PGE, prostaglandin E; SP, substance P; TNF, tumor necrosis factor; LTB, leukotriene B.

Traumeel for modulation of inflammation. In the rat model of microvascular integrity, Traumeel significantly reduced noise-induced venular leakage of fluorescent albumin and degranulation of mast cells, suggesting reduced release of histamine.[58] Noise stress can lead to an excess of reactive oxygen species and inducible nitric oxide synthase (iNOS) in the walls of blood vessels of the cochlea stria vascularis.[59] The antiinflammatory properties of Traumeel were confirmed in animal models of acute inflammation (carrageenan-induced edema) and chronic inflammation (adjuvant arthritis). In these experiments, Traumeel led to a significant reduction of carrageenan-induced hind paw edema in the first model, and during the first week, a reduction of inflammation in the first phase of adjuvant arthritis treatment.[60]

Human research with Traumeel supports its antiinflammatory actions. In an open nonrandomized study of patients with mild rheumatoid arthritis, the influence of Traumeel (15 drops given three times per day for 14 days) on the number of CD4+ T lymphocytes, which are known to secrete transforming growth factor β (an important antiinflammatory cytokine), was studied and evaluated.[61] A moderate increase in CD4+ T-lymphocyte numbers in most patients was observed. The researchers suggested that Traumeel might exert antiinflammatory effects via secretion of transforming growth factor β by these lymphocytes.[61]

Proposed Contribution of Traumeel to Tissue Reorganization

According to Barbe and Barr, the repetitive loading of bones, muscles, and tendons leads to adaptive remodeling of these tissues.[27] Early and discrete tissue injury stimulates an acute inflammatory response that may resolve with tissue repair in the presence of low repetition and low force; this may lead to advantageous adaptive remodeling. However, excessive repetitive loading may cause pathological remodeling/reorganization of tissues (eg, pathological remodeling of bone tissues into immature woven bone at sites of tendon and ligament attachments); myopathic changes, such as denervation and atrophy of muscle fibers, are stimulated, along with a fibrogenic response. This change can result in an increased susceptibility of the tissues to further reorganization and injury, with continued exposure leading

to reduced biomechanical tolerance and continued pathological remodeling. In some cases, there is no evidence of inflammation; in other studies, increased inflammatory cells and myopathic changes were found.[27] Some researchers argue that the interaction between exposure level, anatomical site, and nature of the task produces different tissue responses with respect to magnitude and/or timing.[27]

Some clues about Traumeel's possible contribution to tissue reorganization come from evidence reporting the properties of Traumeel ointment on the healing of experimentally induced wounds (Figure 3). One group of researchers investigated the influence of Traumeel on extracellular matrix (ECM) remodeling and wound healing properties in a coculture model with hepatocytes and hepatic stellate cells in vitro.[62] Traumeel reestablished the wound healing suppressed by the environmental toxin lindane. The researchers concluded that the protective effect of Traumeel may be because of reduced degradation or activated formation of ECM, attenuated migration and/or mobilization of granulocytes, or reduced susceptibility of hepatic stellate cells against lindane.[62] Another research group investigated dexamethasone-depressed wound healing in two rat wound models (namely, incision and dead space). In these experiments, Traumeel showed enhancement in breaking strength in incision wounds and time shortening during the epithelialization period. Moreover, the application of Traumeel locally to the wounds of animals systemically treated with dexamethasone significantly reversed the depressant effect of the steroid on all phases of wound healing.[63] These findings indicate that ECM-producing cells (eg, hepatic stellate cells or fibroblasts) are likely targets for Traumeel's action in enhanced tissue repair and wound healing. Recently, it was reported that Traumeel increased the proliferation of cultured chondrocytes and stimulated glycosaminoglycan release. In addition, Traumeel significantly inhibited matrix metalloproteinase-13 expression, one of the matrix metalloproteinases used in ECM degradation.[64] These effects of Traumeel were independent of each other, suggesting multitargeted action of the preparation toward ECM restoration. Restoration of the proper extracellular environment is an important step in adaptive tissue remodeling; some researchers even suggest a xenogeneic approach for restoring ECM-based scaffolds to promote tissue reconstruction.[65] The important role of ECM-producing cells in tissue remodeling in muscle strain injury[49] and in liver injury[66] is well described. Evidence from the clinical application of Traumeel in the management of muscle strains supports its role in muscle tissue reorganization.[43]

Characteristics of Individual Ingredients of the Traumeel Formula

Traumeel is a complex combination medication, composed of an orchestra of 13 ingredients of natural origin, including plant extracts and minerals. Although a detailed analysis of possible contributions of individual ingredients of Traumeel on a proposed model of work-related MSDs is out of the scope of this article, the literature was reviewed with the aim to identify the characteristic features of these ingredients, which could contribute to Traumeel's

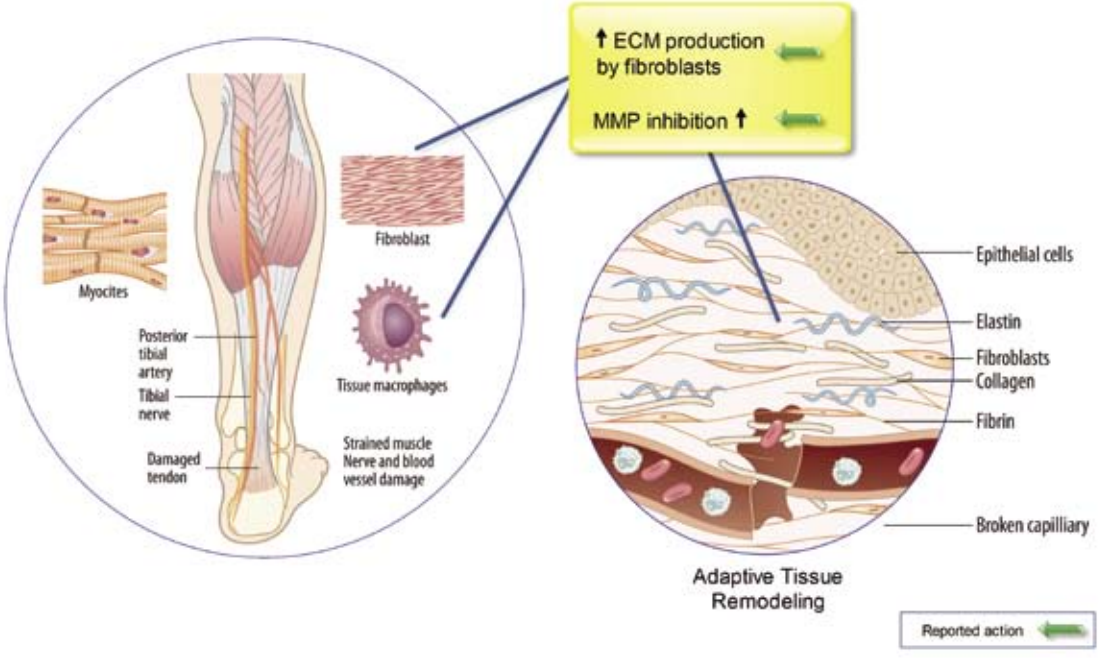

FIGURE 3 Reported Targets of Traumeel's Possible Action in Tissue Reorganization

Traumeel supports adaptive tissue remodeling after tissue injury. Traumeel modulates the function of extracellular matrix–producing cells (eg, fibroblasts and chondrocytes), supports granulation tissue formation, and inhibits some metalloproteinases to reduce tissue degradation. The "Proposed Contribution of Traumeel to Tissue Reorganization" subsection of the "Review of Evidence From Preclinical Research" section provides explanations. ECM indicates extracellular matrix.

TABLE Clinical Characteristics of Ingredients of Traumeel Based on a Literature Review

Properties	*Aconitum*	*Arnica*	*Belladonna*	*Bellis perennis*	*Calendula*	*Chamomilla*	*Echinacea*	*Hamamelis*	*Hepar sulfuris*	*Hypericum*	*Mercurius solubilis*	*Millefolium*	*Symphytum*
Effects													
Immunomodulatory	X[67]	X[67]		X[67]	X[67]	X[67,86]	X[67,87-89]		X[67]	X[67,90]	X[67]		X[67]
Anti-inflammatory		X[68-70]	X[71]		X[91]	X[92,93]	X[71,94]	X[95]		X[96,97]		X[98]	X[99]
Antioxidative					X[72]	X[100]	X[101]	X[102-104]		X[105]		X[98]	
Antinociceptive										X[96,106]			
Antibacterial		X[107,108]		X[109]			X[110]	X[95]		X[111,112]		X[98]	
Antiviral					X[73]			X[113]		X[112]			
Wound-healing					X[74,75]					X[74,114]			X[115]
Mucosa protective												X[116]	
Anti-proliferative					X[117,118]					X[112,119]		X[120]	
Tissue reorganization							X[76,77]						
Anti-hemorrhagic								X[121]					
Spasmolytic					X[122]					X[123]		X[124]	

biological activities. For example, ultra low–diluted *Aconitum napellus* could influence the liberation of transforming growth factor β from leukocytes of healthy donors in whole blood cultures, as do *Arnica montana*, *Calendula officinalis*, *Chammomilla recutita*, *Echinacea*, sulphuric calcium, *Hypericum perforatum*, and *Symphytum officinale*.[67] Moreover, extracts of Arnica flowers show the capability of impairing the activation of the transcription factor nuclear factor κB and the nuclear factor of activated T cells, the proteins that are responsible for the transcription of genes encoding various inflammatory mediators.[68,69] In ultra low doses, pretreatment with *A montana* blocked the action of histamine in increasing vascular permeability.[70] Extracts of *Atropa belladonna* and *Echinacea angustifolia* in ultra low doses modulate the peritoneal inflammation reaction and have a cytoprotective action on leukocytes.[71] Evidence suggests that *C officinalis* exerts free radical scavenging and antioxidant activity.[72] In addition, *C officinalis* may possess some antiviral capabilities.[73] Tinctures of *C officinalis* and *H perforatum* may facilitate the collagen maturation phase of wound healing[74]; on the other hand, an extract from *C officinalis* indicated potent wound-healing activity.[75] Other evidence indicates the antiinflammatory and wound-healing properties of *Echinacea pallida* and its constituent echinacosides.[76] These findings have been confirmed in a pig animal model.[77] The Table provides an overview of the possible clinical characteristics of the ingredients of Traumeel.

These few examples shed some light on the understanding of how different ingredients with multiple biological properties could actually synergize their activities when combined in a complex formula and in a multitargeted fashion to achieve a clinically relevant outcome for a given indication (eg, MSDs).

DISCUSSION

Bioregulatory medicine is a systems-based approach that uses complex medications consisting of activated ultra diluted substances that act in a multitargeted fashion. It allows physicians to adjust the therapeutic regimen to the current condition of the patient. Therefore, the treatment can be adapted to meet the specific needs of the unique stage of an individual's disease. In the present article, the evidence from preclinical studies with the bioregulatory medication Traumeel was used to corroborate the current pathophysiological models of work-related MSDs. The aim was to provide a working hypothesis of the possible mechanisms of action of Traumeel (a multicomponent and multitargeted complex preparation) within such a model. Another aim was to discuss what place bioregulatory therapy can have in the understanding of modern disease evolution and what treatment options this therapy can suggest.

Current scientific knowledge suggests that Traumeel can be a useful addition to the management of work-related MSDs. For example, Traumeel modulates inflammatory pathways by downregulating proinflammatory cytokines and upregulating antiinflammatory cytokines, reducing edema,[60,78] promoting phagocytosis,[55-57] and improving wound healing.[58,62] Adaptive tissue remodeling is supported by Traumeel acting on the behavior

of ECM-producing cells and inhibiting metalloproteinases.[64] This evidence supports and is in line with the pathophysiological model of work-related MSDs; the model suggests that tissue injury, acute inflammation, and tissue reorganization are among the major pathways implicated in the pathophysiological features of these diseases (Figure 4).

It is typical for all biological therapies that their modes of action still need to be fully elucidated. The weakness of the hypothesis of Traumeel's modes of action, suggested in this article, is that many of the proposed biological effects of the individual ingredients of Traumeel have been extrapolated from well-designed studies in botanical medicine that used different

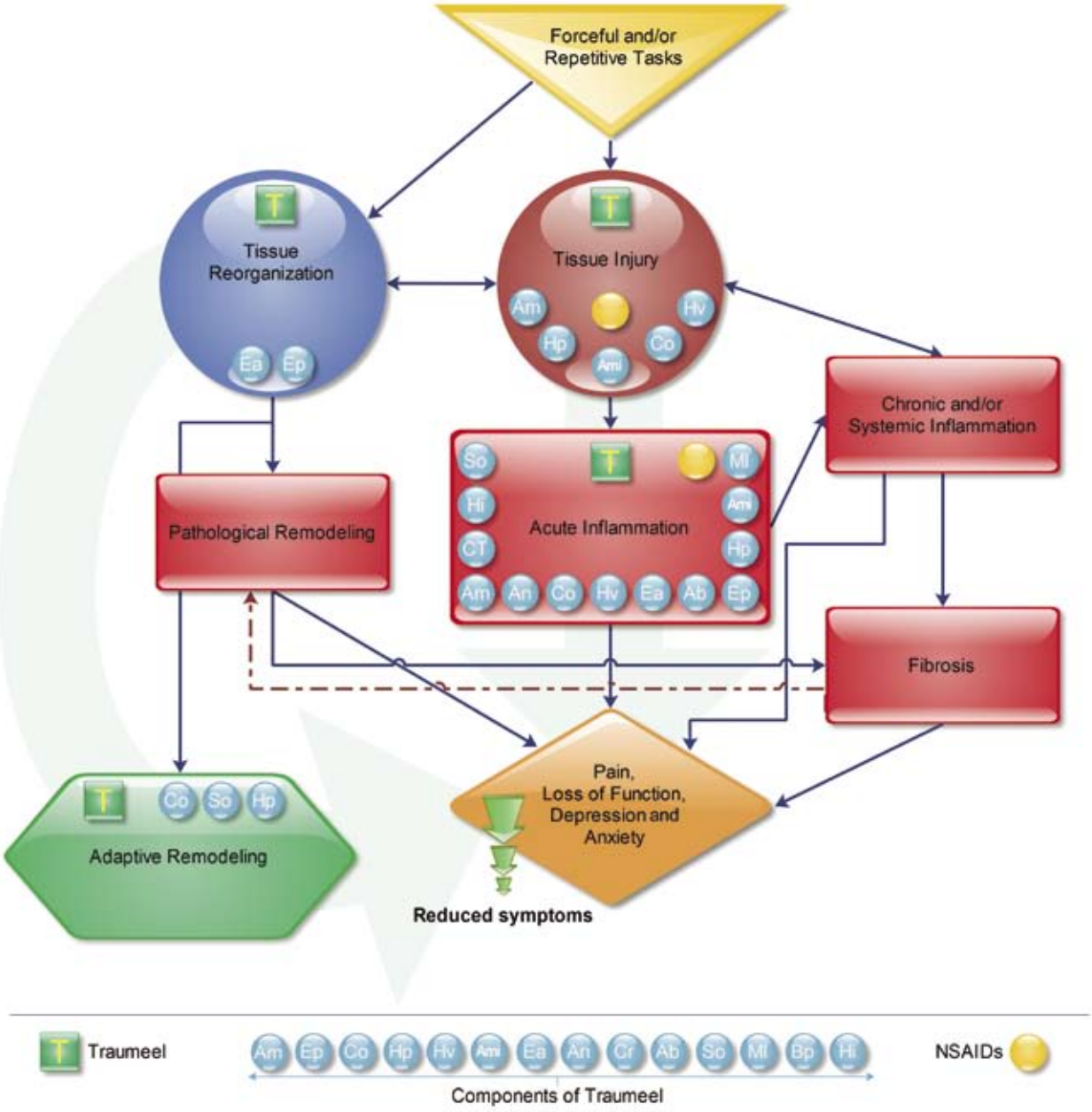

FIGURE 4 Overview of Possible Sites of Action of Traumeel and Its Ingredients in the Pathophysiological Model of Repetitive Overuse Task-related Musculoskeletal Disorders

Traumeel plays a role in multiple pathophysiological processes (inflammation and tissue reorganization). The modulation of these processes toward successful resolution is the key feature of multitargeted action. In contrast, nonsteroidal antiinflammatory drugs act only in distinguished pathophysiological processes (ie, the arachidonic pathway in acute inflammation) by suppressing them. The ingredients of the Traumeel formula are as follows: Ab, *Atropa belladonna*; Am, *Arnica montana*; Ami, *Achillea millefolium*; An, *Aconitum napellus*; Bp, *Bellis perennis*; Co, *Calendula officinalis*; Cr, *Chamomilla recutita*; Ea, *Echinacea angustifolia*; Ep, *Echinacea purpurea*; Hp, *Hypericum perforatum*; Hs, *Hepar sulfuris* (calcium sulfide); Hv, *Hamamelis virginiana*; Ms, *Mercurius solubilis* (mercuro-amidonitrate); So, *Symphytum officinale*. T in the box indicates Traumeel.

doses and preparation forms. Nevertheless, it is possible that the biological targets of these effects might be similar irrespective of the dose. For example, in the case of hormetic-type responses, therapeutic effects swing around the same targets (eg, cell viability/toxicity) but with a different modality (stimulatory/inhibitory) in a nonlinear dose-response manner.[79] In other cases, the effects respond linearly. Crippa et al reported that the combination of endothelial monocyte–activating polypeptide II and TNF-α, both in ultra low doses, synergistically acted on the same target (neovascularization) as in higher doses but showed reduced toxicity.[80] In both cases, the extrapolation of the action of a substance in an ultra low dose is possible given that the target of this action is known. Therefore, the evidence from studies with concentrated plant extracts could provide hints about which molecular networks (not necessarily the same molecular targets) might be the goals of the ultra diluted substances. Evidence from preclinical Traumeel studies supports this notion, showing that the targets of its actions (eg, immunocompetent cells) are also targets of many of its ingredients in plant extract–high concentrations.

There are additional aspects unique to a bioregulatory preparation such as Traumeel regarding its biological targeting features. These aspects include the following: (1) multitargeting, which can be described as a nonlinear summation of biological activities of the ingredients; (2) the fact that multitargeting is necessary to reset the compromised autoregulatory network pattern, in which a multitude of near-threshold stimuli generate several responses and increase autoregulating system robustness; and (3) effectiveness in resolving the pathophysiological pattern, which lies in the synergy of these stimuli and responses. This synergy is not a linear sum of effects of ingredients; rather, it is a specific pattern of biological activities, defined by the combination design of a bioregulatory preparation. Thus, excluding one ingredient from the formula could potentially change the synergistic pattern and alter the properties of a preparation. These features distinguish Traumeel-type preparations from other biological response modifiers, such as infliximab (Remicade), a monoclonal antibody against TNF-α, which has a distinctive mechanism of action of linearly inhibiting one of the master regulators of inflammation-related mechanisms.[81]

The totality of preclinical research suggests that Traumeel has a remarkable scope of action on the pathophysiological processes of work-related MSDs. The strength of the evidence is its role as an immunomodulator. However, there are several potential gaps in its mechanisms of action. For example, despite its broad multitargeted action, Traumeel does not cover all of the pathophysiological pathways of work-related MSDs, as shown in Figure 4. The role of Traumeel as an intervention for central nervous system reorganization still needs to be defined. The coverage of the whole spectrum of pathophysiological events can be achieved by supplementing the treatment with other medications (ie, mainstream and/or bioregulatory preparations) targeted to the modulation of nervous functions. This approach would allow the formulation of treatment concepts with almost complete coverage of all possible pathophysiological networks around any given disorder and would ensure effective and robust resolution of a clinical pathological feature.

Further preclinical studies should be performed with Traumeel to expand the present knowledge of its potential mechanisms of action and to confirm the existing data. The evidence presented herein is still preliminary, and the bioregulation concept itself is in the early stages of development. Nevertheless, the need for discussions exploring scientific assumptions and revealing the gaps in knowledge is widely recognized in the complementary and alternative medicine and traditional medicine communities.[82,83] Further investigations are certainly required to fill these gaps in evidence, using even cutting-edge technologies.

This article presented a specific view on evidence from preclinical research performed with Traumeel, with the aim of providing a plausible hypothesis of mechanisms of action of a complex ultra low–dose medication with bioregulatory properties. Also, the article tries to reflect how the concepts of bioregulation and multitargeting fit to evolving the present understanding of disease complexity and the need to properly address this complexity in a clinical world.

CONCLUSIONS

Increasing scientific knowledge regarding the complexity of biological and physiological processes, boosted by modern technological advances ("-omics" technologies), forces the reevaluation of the current concepts of disease development and moves information from a linear and reductionist view to a complex and network-shaped systems' perception of pathophysiological events defining disease pathogenesis and evolution.[84] The application of systems-based biology concepts in the biomedical field calls for novel therapeutic concepts and approaches that would integrate the systems perspective in the management of complex diseases. Multitargeting is one of these concepts; it allows the application of therapeutic effort to the disease pathophysiological pattern rather than to a single pathophysiological event. Multiple approaches to multitargeting are suggested; the application of bioregulatory therapeutics, which are characterized as combinations of multiple ultra low–diluted substances, is one of them. The current evidence suggests that Traumeel displays nonlinear biological activities in addition to synergistic modes of action and supports its value in treating multifaceted disorders (work-related MSDs) from the systems perspective. Bioregulation is a cutting-edge concept that is increasingly accepted by and integrated into mainstream medical care. Future research will increase the scientific knowledge necessary to support the principal concepts of bioregulatory medicine.

Disclosure

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