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REVIEW ARTICLE

Anti-inflammatory effects of physical stimuli: The central role of networks in shaping the future of pharmacological research

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Addressing complexity in the study of life sciences through Systems Biology and Systems Medicine has been transformative, making Systems Pharmacology the next logical step. In this review, we focus on physical stimuli, whose potential in pharmacology has been neglected, despite demonstrated therapeutic properties. To address this overlooked aspect of pharmacology, we aim to (i), highlight how physical stimuli (mechanical, optical, magnetic, electrical) influence inflammation; (ii) identify known overlaps among transduction mechanisms of physical stimuli and highlight the need for deeper understanding of these mechanisms; (iii) promote advanced network approaches as tools to understand this complexity and enhance the potential of anti-inflammatory physical therapies; and (iv), integrate physical stimuli into the mindset of pharmacologists. The overall purpose of this review is to spark questions rather than provide answers, and to drive research in this critically underexplored area.

KEYWORDS
inflammation, network medicine, physical stimuli

1 | INTRODUCTION

Chronic, low-grade inflammation is a key feature of non-communicable diseases (NCDs), a silent pandemic with a significant societal burden (Saha & Alleyne, 2018). Major efforts (see Sustainable Development Goal 3.4) have been initiated to address chronic inflammation and non-communicable diseases, including the development of new and repurposed drug therapies and lifestyle modifications. Yet, given the limited success in the control of non-communicable diseases, expanding the scope of anti-inflammatory strategies to include physical therapies may represent a safe (Fernández-Guarino et al., 2023), cost-effective (Bürge et al., 2016) and efficient opportunity for repurposing biomedical devices (Karamian et al., 2022).

The use of physical stimuli in clinical settings is not a new concept. The therapeutic potential of electrical stimuli, first recognised by Luigi Galvani (Galvani, 1797), has evolved into what is now known as *electronic biomedicine* (Olofsson & Tracey, 2017). This approach has

Abbreviations: FICZ, 6-formylindolo[3,2-b]carbazole; KEGG, Kyoto Encyclopedia of Genes and Genomes; PN, Petri network; TDA, Topological data analysis.

All authors contributed equally to this work.

primarily targeted specialised nervous system cells paving the way to a new range of therapies known as *vagus nerve stimulation* (VNS). Further, *electroceutical* and *ion channels pharmacology* (Kofman & Levin, 2024) recently followed by *magneto-pharmacology* (Zablotskii et al., 2025) have also been studied. However, these therapies remain mostly experimental.

Mechanical stimuli have applications in orthopaedics and dermatology to enhance tissue repair, and mechanical stimuli have been studied in the contexts of cell stemness, regenerative medicine and oncology (Cezar et al., 2016; Northcott et al., 2018). However, there is limited translation to clinical practice, despite renewed interest in *mechano-pharmacology* (Geesala et al., 2021; Goßmann et al., 2016). Further, anti-inflammatory applications of mechanical stimuli are rare (Avishai et al., 2017; Liu et al., 2023; Nardini et al., 2016).

Optical stimuli were long considered only to affect specialised cells in the retina, until the more recent discovery of specialised fibroblast receptors—**opsins** (Suh et al., 2020). However, limited reports discuss the anti-inflammatory potential of associated clinical approaches (Hamblin, 2017). Despite numerous therapies being defined, from low-level laser therapy (LLLT, Tam et al., 2020) to photobiomodulation (PBM, Leyane et al., 2021; Fernandes et al., 2024), applications remain limited to the realm of experimental medicine (Chen et al., 2023; Stepanov et al., 2022). Finally, magnetic stimuli are perhaps most neglected in the biomedical literature (Miyakoshi, 2005; Zablotskii et al., 2016), despite early interest from prominent figures such as Nikola Tesla (Ristanović, 2016).

The first part of this review will showcase the richness and potential of this research area by exploring different types of physical stimuli and their potential for modulating inflammatory molecules and pathways. We highlight where different types of stimuli overlap in their effects on molecular components of inflammation. To the best of our knowledge, this is a unique contribution.

However, these synergies must be systematically elucidated to take full advantage of the clinical relevance and potential of physical stimuli. Achieving this goal requires integrating knowledge from currently compartmentalised research areas. Thus, the second part of this work provides an overview of network approaches applied to pharmacology and inflammation, capable of modelling the complex nonlinearities typical of biological systems, that have been applied to pharmacology and/or inflammation. Direct applications of network approaches to physical stimuli represent a key gap we discuss in this article, and therefore explicit examples are not currently available. Therefore, we provide an overview of the methodological possibilities available to encourage researchers to undertake this path. Additionally, we discuss applications that hold promise for translation to the research field of physical transduction.

Overall, by presenting the anti-inflammatory effects of physical stimuli and the potential of network approaches in advancing pharmacology, we outline a pathway to bridge the gap in the exploitation of physical stimuli as anti-inflammatory therapies.

2 | PHYSICAL TRANSDUCTION AND INFLAMMATION

2.1 | Mechanical stimuli

Mechanical stimuli are diverse and can be classified by mode of application, including manual approaches such as massage and acupuncture or biomedical device-based methods such as negative pressure, vibrations and ultrasound. Mechanical stimuli can also be classified by the downstream forces acting on cells (shear stress, pressure, stiffness, stretch, etc.). In addition, within each mode of application, parameters such as intensity, frequency and duration of the stimulus can vary. Here, we discuss in more detail two exemplars of mechanical stimuli: - low intensity vibration (LIV) and ultrasound.

Low intensity vibration, defined as vibrations with accelerations (i.e. a measure of the impact of vibrations) < 1 g and frequencies < 60 Hz, has been shown to reduce inflammation, improve wound healing and reduce tumour growth. In particular, low intensity vibration can improve angiogenesis, blood flow and skin wound healing in diabetic mice and can potentially inhibit progression of pressure ulcers by reducing negative aspects of inflammation and increasing growth factor activity (Haba et al., 2023; Roberts et al., 2023). Interestingly, whole body low intensity vibration increases **insulin-like growth factor 1 (IGF1)** protein levels not only in wounds of diabetic mice but also in liver and blood. Because the liver is a primary source of both circulating IGF1 and IGF1 in skin wounds, inducible ablation of IGF1 in liver was used to determine whether liver IGF1 mediates effects of low intensity vibration on wound healing (Roberts et al., 2023). Indeed, knockdown of IGF1 in liver blunts low intensity vibration-induced improvements in wound healing in high-fat diet-fed mice, including angiogenesis and granulation tissue formation. In addition, whereas low intensity vibration reduced neutrophil accumulation and **interleukin-1 beta (IL-1β)** levels in wounds, this anti-inflammatory effect of low intensity vibration again appeared to be liver-IGF1 dependent.

Further, exercise is known to have beneficial effects on non-communicable diseases, and low intensity vibration is often used as an exercise mimetic. In a recent study, low intensity vibration was used as a potential therapy for inhibiting development of intestinal cancer in adenomatous polyposis coli gene. $(Apc)^{Min/+}$ mice (Iwata et al., 2023). Low intensity vibration was associated with a reduction of the percentage of large polyps and increased the villi/crypt ratio compared to controls, which was used as a marker of inflammation, suggesting that low intensity vibration correlates with suppressed local inflammation and polyp growth in the small intestine.

Another type of mechanical stimulus, ultrasound (Figure 1a), has been a cornerstone of clinical practice for over a century, serving both diagnostic and therapeutic purposes. Therapeutic applications rely on mechanical acoustic energy that can be modulated by parameters such as frequency, intensity, duration, duty cycle and treatment count. Depending on these parameters, ultrasound can induce either thermal or non-thermal bioeffects, such as microstreaming (localised fluid flow induced by ultrasound vibrations) and non-inertial acoustic cavitation

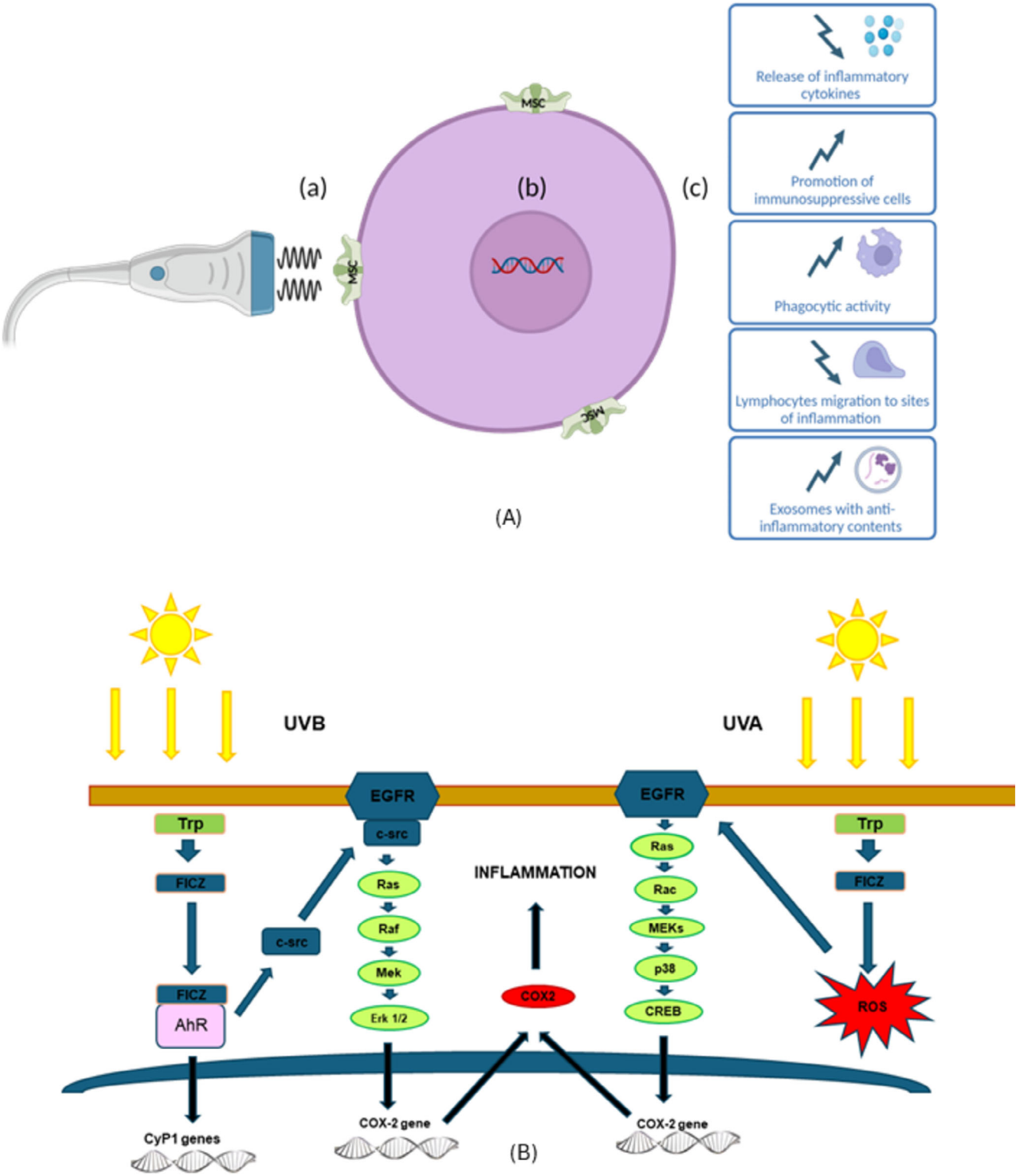

FIGURE 1 Legend on next page.

(stable bubble oscillations without collapse in response to acoustic waves, Jiang et al., 2019).

The unique properties of therapeutic ultrasound have been leveraged for various medical applications, including drug delivery, neuromodulation and non-invasive procedures for surgery and cancer therapy (De Maio et al., 2024; Feng et al., 2024; Nowak et al., 2022; Zhang et al., 2022). Recent studies highlight ultrasound's potential to elicit anti-inflammatory responses and promote tissue regeneration, as long as parameters are selected to minimise adverse thermal effects. Low-intensity continuous or pulsed ultrasound (LICUS and LIPUS, respectively) is commonly employed, using frequencies of 1–3 MHz, intensities below 3 W/cm^2 and durations of 5 to 20 min (Jiang et al., 2019; Uddin et al., 2021). Under these conditions, ultrasound's anti-inflammatory effects may be explained by mechanotransduction-like modes of action, where cells convert mechanical strain into biochemical signals, eventually leading to altered gene expression and/or release of signalling molecules (Oliveira et al., 2023). Immune cells, particularly macrophages, are influenced by ultrasound signals, via mechanosensitive ion channels such as **Piezo1** and **TRPV1**. In pro-inflammatory macrophages, these channels may modulate **p38 MAPK** signalling pathways and attenuate the release of inflammatory cytokines (Iacoponi et al., 2023). Mechanical ultrasound signals have also been shown to facilitate neutrophil clearance by significantly boosting M2 macrophage-mediated phagocytosis (Chung et al., 2016) and to induce transcriptional modulations in splenic T and B lymphocytes, reducing their migration to inflammatory sites (Zachs et al., 2019). Further ultrasound effects include the increased production, release and docking of exosomes containing anti-inflammatory cytokines and microRNAs, as well as the promotion of immunosuppressive cells such as myeloid-derived suppressor cells, mesenchymal stem cells, B1-B cells and regulatory T cells (Yang et al., 2017).

2.2 | Optical stimuli

Transduction of optical stimuli was long thought to be confined to the visual system via the specialised receptors of the retina (rods and cones). However, recent advances suggest opto-sensors are present in various tissues and organs involved in processes dependent on light/dark alternation, including the skin. Considering the significant potential for medical translation, this section focusses on skin opto-transduction, which is the process by which skin cells convert visible light (400–750 nm) and ultraviolet radiation (UV, 200–400 nm) into biochemical signals. The best-known light-related phenomenon in skin is melanogenesis, which protects mammals from the harmful effects of UV sunlight radiation. However, an extensive body of literature documents the presence of chromophores and photosensitisers in skin that play crucial roles in light-sensitive processes across various fields including biology, photochemistry and phototherapy.

Human skin, in particular the epidermis, contains several major solar ultraviolet radiation (UVR)-absorbing endogenous chromophores including urocanic acid, DNA and some amino acids among which is **tryptophan (Trp)**, 7-deydrocholesterol and **melanin** with their precursors and metabolites (Young, 1997). These molecules absorb light at particular wavelengths and transform its physical energy into chemical energy, which is transferred to nearby molecules. In this manner, they can trigger or halt biochemical processes while maintaining stability and avoiding the production of reactive oxygen species (ROS). Also, these molecules can contribute to photo-biomodulation (PBM) therapies which can enhance cellular metabolism and promote healing processes (Leyane et al., 2021).

Skin photosensitisers can also transfer absorbed energy to other molecules, generating ROS and damaging nearby molecules and cells. Photosensitiser properties can be targeted by photodynamic therapies for the treatment of melanomas or other pathogenic cellular formations (Huis in 't Veld, 2023). In this context, 6-formylindolo[3,2-b] carbazole (FICZ) is formed by UV-mediated photo oxidation of tryptophan (Trp). Thanks to the pioneering work of Rannug's group, the properties of FICZ have been linked to the activation of **aryl hydrocarbon receptor (AhR)**, a ligand-activated transcription factor that mediates the response to numerous exogenous and endogenous stimuli (Rannug et al., 1987). FICZ is the most potent endogenous agonist for aryl hydrocarbon receptor, which on one hand sustains the transcription of cytochromes **CYP1A1**, **CYP1A2** and **CYP1B1** that regulate detoxifying functions and keep skin FICZ concentration low, but on the other hand also induces **src**-mediated activation of the inflammatory pathway **EGFR**-**ERK1**/**2**-**COX-2**. Notably, c-src is part of the cytoplasmic complex that inactivates aryl hydrocarbon receptor and, once detached following aryl hydrocarbon receptor activation,

FIGURE 1 (Panel A) Modulation of anti-inflammatory pathways via therapeutic ultrasound (see Section 2.1). With the application of (a) fine-tuned low-intensity ultrasound, mechanotransductive pathways are activated through mechanosensitive channels (MSCs) within (b) target cells. This engagement may initiate a reduction in inflammatory cytokine production and prompts an increase in the populations of immunosuppressive cells. Additionally, it may enhance macrophage phagocytosis, decrease lymphocyte infiltration to inflamed tissues and escalate the release of exosomes laden with (c) anti-inflammatory agents. These sequential actions illuminate the nuanced mechanistic interplay orchestrated by ultrasound, highlighting its potential for targeted anti-inflammatory therapy (figure created with BioRender.com). (Panel B) UVA and UVB radiations effects on skin tryptophan (Trp) converge to inflammation (see Section 2.1). Upon UVB exposure, photosensitive tryptophan is transformed into FICZ which binds to aryl hydrocarbon receptor (AhR). This causes the detachment of c-src from the AhR inactivating complex. Then, c-src activates EGFR and the downstream signalling pathway Ras-Raf-MEK-Erk 1/2, resulting in the transcriptional activation of gene COX-2. In parallel, active AhR is translated to the nucleus where it stimulates the transcription of CYP1 genes. The exposure to UVA radiation photosensitises FICZ and favours the formation of ROS that sustain the ligand-independent activation of EGFR. The EGFR downstream pathway Ras-Rac-MEKs-p38 leads to CREB activation and translation in the nucleus, where it activates the transcription of gene COX-2.

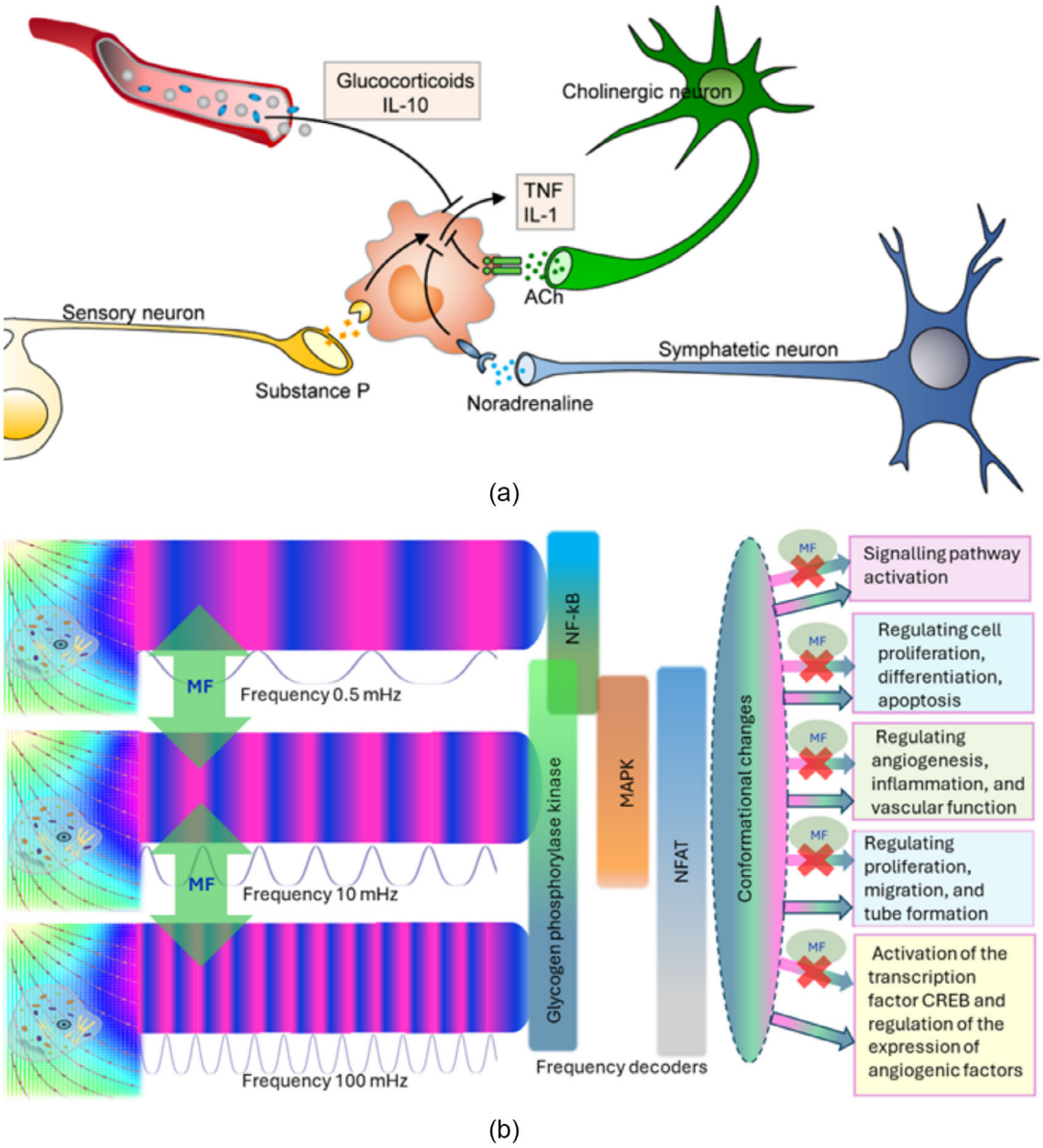

FIGURE 2 (a) Reproduced with permission from Maturo et al. (2020)), circulation delivers inflammatory molecules and cells and diffusible factors bidirectionally between blood and site of inflammation. Cholinergic and noradrenergic neurons, whose neurotransmitters predominately inhibit inflammation response from immune cells have local and fast action. Sensory neurons enhance the inflammatory response by stimulating cytokines production and release. (b) Frequency modulation of Ca^{2+} waves and magnetic switching of metabolic pathways in endothelial cells are depicted with four frequency decoders shown: NF-kB, MAPK, NFAT (nuclear factor of activated T-cells) and glycogen phosphorylase kinase (Smedler & Uhlén, 2014). A magnetic field (green vertical arrows and spots marked with magnetic field [MF]) switches the frequency bands of Ca^{2+} waves, thereby changing/closing enzyme activity and metabolic pathways. Reproduced with permission from Gorobets et al. (2024)).

phosphorylates, the epidermal growth factor receptor (EGFR) that gives rise to an important inflammatory pathway in skin (Fritsche et al., 2007). If activated by UVA, FICZ behaves as a powerful skin photosensitiser (Park et al., 2015). This occurs independently of a direct interaction with aryl hydrocarbon receptor and leads to downstream oxidative signalling. ROS activate EGFR in a ligand-independent way and trigger the Ras-Rac-MEKs-p38 pathway, leading to CREB-mediated transcriptional activation of gene cyclooxygenase-2 (*PTGS2*), a key player in inflammatory signalling (Syed & Mukhtar, 2015), see for an overview Figure 1B. Interestingly, in 2017, Furue's group showed that FICZ increases the expression of Interleukin 1α, 1β and 6 (**IL-1α**, **IL-1β** and **IL-6**) in UVB-exposed HaCaT keratinocytes cells through an aryl hydrocarbon receptor-dependent oxidative stress. In these inflammatory conditions, the interaction between FICZ and aryl hydrocarbon receptor is associated with a positive action on skin barrier, as evidenced by an increase in loricrin, involucrin and filaggrin, three proteins belonging to the skin epidermal terminal differentiation (Furue et al., 2019). Interestingly, *in vivo* experiments demonstrated that FICZ drives the differentiation of T helper cells (Th or CD4+) towards a Treg immunosuppressive or

a Th17 inflammatory phenotype, with the outcome being dependent on the dosage and duration of the application. Recently, Baglole's group reported the activation of aryl hydrocarbon receptor and its immune modulatory action following UVB exposition even in organs not directly exposed to solar radiation. This is consistent with the hypothesis of an endocrine role for aryl hydrocarbon receptor, linking immune functions to sunlight exposure (Memari et al., 2019). FICZ has also been characterised as a sensitiser to blue light, which is known for its potent inhibition of melatonin synthesis. Intriguingly, **melatonin**, whose production rises when natural light decreases, is an agonist of aryl hydrocarbon receptor and the **peroxisome proliferator-activated receptor γ (PPAR-γ/NR1C3)** in human keratinocytes. These interactions likely counterbalance the high oxidative stress consequent to a protracted exposition to solar radiation and contribute to melatonin cytoprotection, which is favoured by the stimulation of cellular differentiation and barrier functions promoted by PPAR-γ in keratinocytes (Slominski et al., 2023).

2.3 | Electric stimuli

The impact of electric stimulation on inflammatory pathologies has received significant attention in the biomedical literature. However, the delivery methods and stimulation parameters (frequency, voltage and duration) used in studies on both animal models and humans are extremely heterogeneous (Di Pietro et al., 2024; Di Pietro et al., 2025). Nevertheless, a putative unifying framework includes the ability of the different stimulation modalities to modulate neuroimmune interactions, guiding these towards an anti-inflammatory outcome (Figure 2a).

The method of choice for administering therapeutic electrical stimulation is transcutaneous electrical nerve stimulation (TENS). Although transcutaneous electrical nerve stimulation has been used primarily to manage acute or chronic pain (Gibson et al., 2019), it has also been shown to have anti-inflammatory effects (do Carmo Almeida et al., 2018). Because transcutaneous electrical nerve stimulation targets nerves, it is reasonable to assume that the anti-inflammatory effect of transcutaneous electrical nerve stimulation results from modulating interactions between nervous and immune systems. Such interactions can be influenced by transcutaneous electrical nerve stimulation through the modulation of both peripheral and central nervous activity. High-frequency transcutaneous electrical nerve stimulation significantly reduces the release of aspartate and glutamate in the spinal cord dorsal horn in animals with joint inflammation. This reduction is mediated by the activation of **opioid δ receptor**, which suggests a peripheral neurochemical pathway through which transcutaneous electrical nerve stimulation exerts its anti-inflammatory effects (Sluka et al., 2005). This hypothesis is supported by experiments showing that electrical stimulation of the dorsal root ganglion (DRG) may prevent inflammation and joint damage in conditions such as rheumatoid arthritis, by interrupting neurogenic inflammation (Pan et al., 2018). However, both high- and low-frequency transcutaneous electrical nerve stimulation can reverse mechanical hyperalgesia induced by muscle inflammation, suggesting the activation of a central mechanism involving spinal and supraspinal sites (Ainsworth et al., 2006). The cholinergic anti-inflammatory pathway (Borovikova, Ivanova, Nardi, et al., 2000; Borovikova, Ivanova, Zhang, et al., 2000) has been identified as a primary central target for electrical stimulation. Neurostimulation of this pathway has been shown to ameliorate disease severity in rat models of collagen-induced arthritis (Levine et al., 2014). Specifically, vagus nerve stimulation (VNS) resulted in significant reductions in joint swelling, histological arthritis scores and serum levels of pro-inflammatory mediators such as receptor activator of **NF-κB** ligand **RANKL** (Levine et al., 2014). In models of splanchnic artery occlusion (SAO) shock, activation of the cholinergic anti-inflammatory pathway through electrical stimulation of efferent vagus nerve suppressed the inflammatory cascade, leading to increased survival rates, reduced hypotension and decreased levels of pro-inflammatory cytokines such as **TNF-α** (Altavilla et al., 2006).

The vagus nerve is a central player in cholinergic anti-inflammatory pathways (Borovikova, Ivanova, Zhang, et al., 2000; Caravaca et al., 2019; Kelly et al., 2022; Tracey, 2002). Vagus nerve stimulation mediates protection from kidney ischaemia-reperfusion injury through **α7 nicotinic acetylcholine receptor (α7nAChR+)**-positive splenocytes, highlighting the role of the cholinergic anti-inflammatory pathway in modulating innate and adaptive immunity (Inoue et al., 2016). Interestingly, vagus nerve stimulation blunted the systemic inflammatory response to endotoxin by significantly reducing the release of cytokines like TNF-α, IL-1β, IL-6 and **IL-18**, while not affecting the anti-inflammatory cytokine **IL-10** (Borovikova, Ivanova, Zhang, et al., 2000). Transcutaneous vagus nerve stimulation was also effective in reducing serum **high mobility group box 1 (HMGB1)** levels and improving survival in murine sepsis (Huston et al., 2007). Vagus nerve stimulation has been shown (Falvey, 2022) to attenuate cytokine production and macrophage activation, which are key players in the inflammatory response. This anti-inflammatory action is mediated through distinct mechanisms involving both vagal efferent and afferent neurons. Vagal efferent neurons, when activated, can ameliorate sepsis-induced inflammation through acetylcholine derived from T-cells, while afferent neurons can reduce inflammation independently of T-cell derived acetylcholine. Vagus nerve stimulation has also been found to produce an anti-inflammatory monocyte phenotype in blood, reducing the proportion of circulating pro-inflammatory monocytes and dendritic cells (Kaur et al., 2023).

Similar to the stimulation administered via transcutaneous electrical nerve stimulation, a large amount of data has been published on the anti-inflammatory properties of electroacupuncture (EA) (Pan et al., 2021; Park & Namgung, 2018; Ulloa et al., 2017). Interestingly, the mechanisms underlying the anti-inflammatory therapeutic efficacy of transcutaneous electrical nerve stimulation and electroacupuncture appear to result from the same neurophysiological pathways (Cabioğlu & Cetin, 2008; Pan et al., 2021).

Transcranial direct current stimulation (tDCS), originally aimed at the treatment of pathologies of the central nervous system, has been shown to induce the activation of physiological mechanisms that counteract the onset and/or propagation of inflammatory states, in

both central and peripheral fields (Leffa et al., 2018). In an orofacial pain model, anodal transcranial direct current stimulation reduced nociceptive behaviour and altered levels of neuro-immunomodulators such as **brain-derived neurotrophic factor (BDNF)**, **nerve growth factor (NGF)**, IL-6 and IL-10 in the brainstem, further supporting the potential modulatory effects of transcranial direct current stimulation on the strict interplay between mechanisms controlling pain sensitivity and inflammation (Scarabelot et al., 2019). Transcranial direct current stimulation was also shown to alter the expression of immune-mediating genes in somatosensory cortices, with anodal stimulation increasing the expression of genes coding for major histocompatibility complex I and cathodal stimulation increasing the expression of the immunoregulatory protein **osteopontin** (Rabenstein et al., 2019). On the peripheral side, a study conducted in older adult patients with knee osteoarthritis demonstrated that anodal transcranial direct current stimulation, applied over the motor cortex contralateral to the affected knee, was associated with reduced levels of inflammation, as indicated by lower serum levels of IL-6, IL-10, TNF-α and **β-endorphin** compared to sham transcranial direct current stimulation (Suchting et al., 2020).

2.4 | Magnetic stimuli

Magnetic fields have long been used in attempts to improve tissue regeneration, induce analgesia and reduce inflammation. However, magnetic fields have been applied in clinical practice without sufficient scientific justification and understanding of the mechanisms involved. Recently, progress in magnetobiology and development of new magnetic systems that enable greater control of magnitude and spatial configuration allow for the targeting of different biological processes, such as the production of ROS (Zablotskii et al., 2023), DNA synthesis (Yang et al., 2020), induction or suppression of anti-inflammatory cytokines (Kim et al., 2023), modulation of ion channel activity and membrane potential (Zablotskii et al., 2023), induction of apoptosis in cancer cells (Zablotskii, Syrovets, et al., 2014) and alteration of stem cell differentiation (Zablotskii, Lunov, et al., 2014). In short, the magnetic field is a non-invasive and reversible physical tool that can penetrate tissues and cells to selectively control cell machinery.

In particular, calcium (Ca^{2+}) signalling plays a crucial role in various cellular processes, including those involved in inflammation. Indeed, Ca^{2+} signalling and inflammatory effects are related through several mechanisms, including the activation of immune cells, such as macrophages, dendritic cells and lymphocytes; the production and release of pro-inflammatory cytokines such as IL-1, IL-6, TNF-α and others; the chemotaxis and migration of immune cells to sites of inflammation; and the phagocytosis and oxidative burst and the balance between cell death (apoptosis) and cell survival in inflammatory responses. Malfunctioning of ion channels, including Ca^{2+} channels, plays a crucial role in various diseases. However, the availability of approved drugs targeting ion channels directly still remains limited. Over the past three decades, efforts to find drugs have been hampered by the complexity of achieving selectivity and specificity for ion channels, given their pervasive distribution on cells.

As an alternative to pharmaceutical approaches, the development of physical methods for influencing ion channels is being studied (Gorobets et al., 2023). The possibility of selectively controlling Ca^{2+} channel activity and Ca^{2+} signalling with magnetic fields is an attractive approach (Gorobets et al., 2024), by applying either a time-varying or static gradient magnetic field (MF). This involves exerting magnetic forces or torques on biogenic or non-biogenic magnetic nanoparticles bound to endothelial cell membranes. The suggested magnetic treatment offers the potential to regulate the decoding of Ca^{2+} signals, thereby influencing protein synthesis. Figure 2b illustrates the ability to modulate Ca^{2+} wave frequencies using magnetic fields and the magnetic field-controlled decoding of Ca^{2+} signalling. This opens perspectives for clinical applications, in particular, modulating the transmission of the Ca^{2+} signals may help to reduce inflammation in autoimmune diseases by regulating the function of immune cells (Feske, 2007).

Rotating magnetic fields (RMF) have also been used to modulate Ca^{2+} concentrations. Human umbilical vein endothelial cells (HUVECs) and *Caenorhabditis elegans* were exposed to a rotating magnetic field (0.2 T and 4 Hz, Xu et al., 2019), resulting in an extended lifespan of *C. elegans* and decelerating the ageing process of HUVECs. Treatment of HUVECs with rotating magnetic field revealed that activation of **adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK)** led to a decline in mitochondrial membrane potential, attributed to elevated intracellular Ca^{2+} concentrations induced by endoplasmic reticulum stress in anti-ageing mechanisms.

Importantly, very high non-uniform (gradient) static magnetic fields can negatively impact the course of certain serious illnesses. For example, it was recently shown that a 14-h exposure of diabetic mice to a static magnetic field (9.4 T with a gradient larger than 10 T/m) caused harmful effects in severe T1D mice, which may be correlated to oxidative stress and inflammation induced by persistent hyperglycaemia (Yu et al., 2023).

3 | INTEGRATION, WHERE ARE WE?

In Sections 2.1–2.4, we show that various stimuli—mechanical, optical, magnetic and electric—influence inflammatory processes and share several common features in their mechanisms of action. Despite being distinct in their nature, they all interact with cellular and molecular systems in ways that modulate inflammation. In the following, we summarise key shared effects for each stimulus type.

The anti-inflammatory effects of low intensity vibration and ultrasound share conceptual and mechanistic parallels with the other physical stimuli, particularly their engagement with downstream immune-modulatory pathways. For instance, while low intensity vibration modulates inflammation through IGF1-dependent pathways to enhance tissue repair and optical stimuli utilise chromophores activation for photo-biomodulation, ultrasound employs mechanotransduction mechanisms via mechanosensitive ion channels (e.g. Piezo1 and

TRPV1). For ultrasound, such activation cascades into signalling pathways such as p38 MAPK, which reduces pro-inflammatory cytokine release; this pathway can also be activated by low intensity vibration. Interestingly, similar to optical stimuli, which influence T cell polarisation and cytokine modulation via aryl hydrocarbon receptor activation, ultrasound and low intensity vibration can modulate immune cell behaviour, enhancing anti-inflammatory activity of macrophages and Tregs. Mechanistic overlap between these physical stimuli include cytokine regulation, immune cell recruitment and signalling pathway convergence. Thus, there appears to be a shared framework of biophysical stimulus transduction.

While optic stimuli rely on photochemical reactions, mechanical stimuli on physical deformation, magnetic stimuli on electromagnetic energy, electrical stimuli on ion fluxes and membrane potential modifications, all have the ability to induce cellular stress responses, leading to inflammatory modulation. All these stimuli modulate the synthesis and activity of key cytokines, that is, IL-1β, IL-6 and TNF-α, in inflammatory responses. These stimuli directly affect immune cells: optic stimuli promote differentiation of T cells (Guarnieri, 2024), electric stimuli reduces pro-inflammatory macrophage activity (Bao et al., 2024) and mechanotransduction enhances the migration of leukocytes (Gráczer et al., 2024). Finally, all these stimuli converge on the activation of the NF-κB and mitogen-activated protein kinase (MAPK) pathways (Chu et al., 2024). These stimuli also activate cellular stress responses, including ROS production and antioxidant responses (Hamblin, 2017; Momin et al., 2024; Pribil Pardun et al., 2024). Overall, these parallels suggest a fundamental biological responsiveness of immune cells to different physical stimuli.

Different physical stimuli may also share downstream mechanisms involving the nervous system. The anti-inflammatory effect of electrical stimulation likely involves the nervous system and its interplay with the immune system, termed neuro-immuno-modulation. Electrical stimuli induce a general down-regulation of monocytic activity and the release of inflammatory cytokines, via modulation of the nervous system activity through the intracellular and trans-membrane mobilisation of Ca^{2+} ions. This mechanism is shared with downstream effects of magnetic stimulation. In addition, the modulation of the ion channel TRPV1 can be seen as a common mechanism leading to reduced inflammation and inflammatory pain, triggered by both electrical (Xu et al., 2024) and mechanical stimuli (Iacoponi et al., 2023) as well as magnetic stimuli (Zablotskii et al., 2025).

Finally, low intensity vibration and magnetic vibrations share mechanisms of action. For instance, low-magnitude mechanical signals have been shown to inhibit the differentiation of bone marrow cells into adipocytes (Rubin et al., 2007), much like low-frequency magnetic vibrations suppress the differentiation of mesenchymal stem cells into adipocytes (Zablotskii, Lunov, et al., 2014). This correlation is not surprising, as magnetic forces essentially function as mechanical forces on cells and their organelles, inducing deformation of the cell membrane. Such deformation, in turn, influences the expression of mechanosensitive channels and alters the membrane potential (Gorobets et al., 2024), thereby impacting the cell differentiation pathway.

In summary, physical stimuli induce anti-inflammatory effects via the activation of mechanosensitive ion channels, leading to alterations in ion homeostasis, cytokine release, immune cell activity, and tissue regeneration and repair. However, this characterisation remains empirical, qualitative and incomplete. Studies to date have lacked standards for experimental methodologies *in vitro* and *ex vivo;* in pathway representations; and treatment protocols and scientific reporting, which yield inconsistent and occasionally contradictory, results and prevent powerful meta-analyses. In addition, the breadth of the mechanisms involved and the complexity of their interactions cannot be easily captured by manual case-by-case observation.

We posit that a leap forward in our understanding of the impact of physical stimuli on inflammatory processes can only be achieved by integrating available knowledge in a systemic way. Systems approaches encourage integration of large amounts of information, whose numerosity, complexity and heterogeneity can be modelled using networks (a.k.a. graphs-)-based approaches. These approaches can make sense of such richness with a diversity of specialised mathematical and computational approaches, each able to capture different features of the system.

In the following sections, we present four network graph-based approaches for the modelling of biological systems focussing on the molecular and cellular level of integration. These approaches form the bases against which data can be compared to assess medical effectiveness and guide clinical dosage. Examples of applications are presented, comparing different approaches on the same network representation, while maintaining focus on the theme of inflammation. Whereas physical stimuli are the topic of our article, network applications in this area are limited and represent an important gap to be filled. The structure of the following discussion is depicted in Figure 3.

4 | SYSTEMS VIEW: NETWORK APPROACHES AND APPLICATIONS

Systems biology and network medicine have long highlighted the importance of graph-based approaches in the identification of *emergent properties*, which are characteristics that can be observed only when the system of interest is studied in its entirety.

Networks/graphs offer the possibility to model dynamic events and complex static relations and to identify robust patterns that are correlated to relevant parameters of the system under study. These approaches have proven to be useful in biomedicine, as will be shown below. In the next section of this article, we will present four major graph-based approaches applications used to elucidate mechanisms of inflammation or explore pharmacological issues.

4.1 | Static network representation and topological analysis

Established approaches to network biology involve the formalisation of complexity as the connections among molecules (nodes) via their

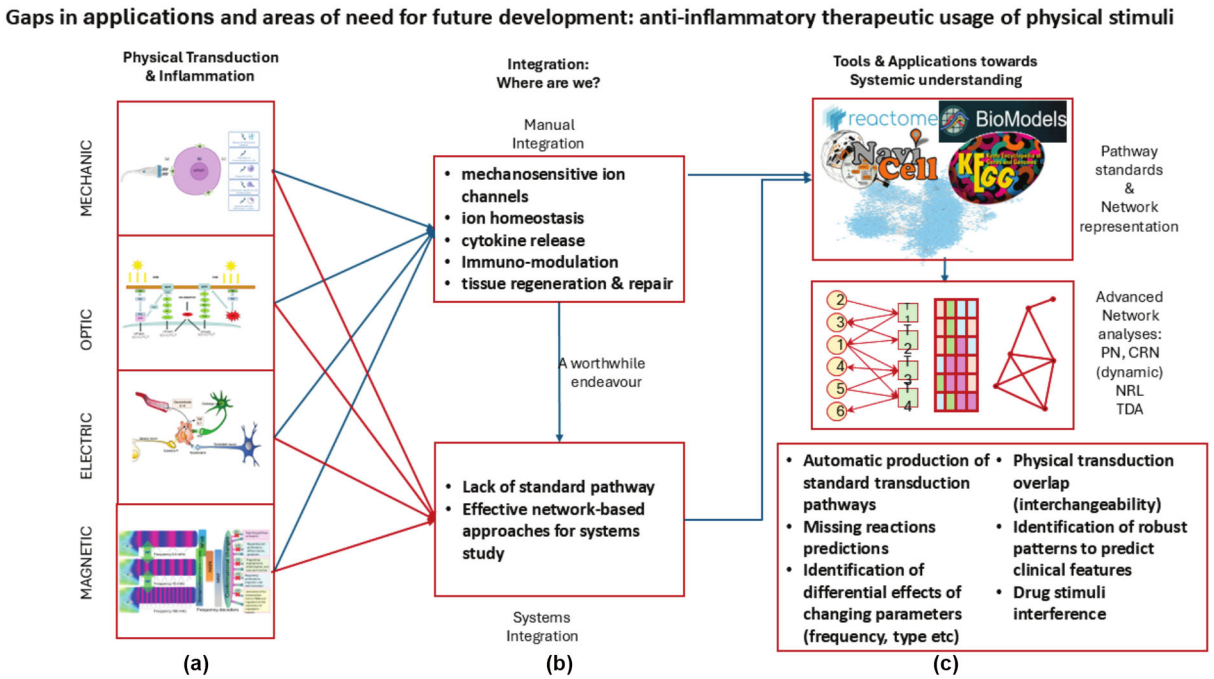

FIGURE 3 Graphical representation of the organisation of the current review. (a) Presentation of current knowledge on the anti-inflammatory effects of physical stimuli (mechanic, optic, electric, magnetic) as described in Section 1. (b) Bridging Section 2: state-of-the-art on the known overlaps and potential synergies among physical stimuli transduction and inflammatory pathways. This knowledge represents a proof-of-concept of the importance of exploring such overlaps in a systematic way. To achieve this goal, the support of powerful formalisms able to manage complexity is necessary. Network-based approaches are introduced as high potential tools in Figure 3. Biological pathways and protein–protein interaction (PPI) networks represent the main knowledge base for the identification of relevant information in biology. Standardised approaches backed by manual curation guarantee the quality of the information input. Dynamic simulation can be run with chemical reaction networks (CRN) and Petri network (PN); identification of non-trivial and robust patterns for drug repurposing and meaningful correlates with clinical parameters can be identified with network representation learning (NRL) and topological data analysis (TDA). Exemplar results of network-based approaches applications include the identification of differential effects of external stimuli, drug repurposing approaches exploiting physical transduction effectors as drug targets and robust patterns identification to predict clinical outcome.

reactions (edges) or other types of association (for example, co-expression). These approaches are extremely flexible and we here present two main types of static networks. The first is protein–protein interaction (PPI) networks. These are classic examples in network (systems) biology that aim to describe proteins and their relationships by connecting the interacting ones only, for example, because of hydrogen bonding or electrostatic forces among them.

Other common networks in biology involve the representation of pathways. For these approaches, standardisation of pathway representation is important to achieve high-quality results. However, most graphical representations of pathways are presented in the form of cartoons. Although this allows representation of a large number of molecules, such formats are unstandardised, making peer review, corrections and extension cumbersome. To overcome this issue, efforts are being made towards the creation of standards. The Co. MBINE initiative (https://co.mbine.org/#about) maintains standards for pathway representations, among which the systems biology markup language (Systems biology markup language, Keating et al., 2020) is popular. Systems Biology Graphical Notation (SBGN, Le Novere et al., 2009) accompanies the standardised representation of pathways and has been adopted by a number of highly accessed pathway repositories including Reactome (Jassal et al., 2020), Kyoto Encyclopedia of Genes and Genomes (KEGG) (Kanehisa et al., 2016), Navicell (Kuperstein et al., 2013), Biomodels (Malik-Sheriff et al., 2020) and Minerva (Gawron et al., 2016). Crucially, these standards are both human and machine readable and thus facilitate interpretation and automatic processing. Once this first level of abstraction (from biology to standard pathways and is protein–protein interaction) is achieved, numerous tools can import pathways within the network formalism (one for all Cytoscape by Killcoyne et al., 2009) to extract various types of characteristics (see Supporting Information). In the following, we explore how these representations constitute a flexible biological knowledgebase, ready for elaboration with advanced network-based approaches.

We present here three applications: the first is one of the few examples of networks modelling physical transduction, that is, the pathway of mechanotransduction, recently updated to explicitly include the innate immune response (Suriyagandhi et al., 2024). Upon manual conversion of the natural language description from scientific literature, the network models explicitly different types of mechanical stimuli (*shear stress* or *stretch* for example). These network analyses showed that the stimuli explored share impact on inflammatory and

proliferative activity, with some differences: *shear stress* correlates with G2M checkpoint activity, while *stretch* may be associated with milder effectiveness when compared to other stimuli. Also RAC1 emerges as a relevant molecule (as a biomarker or a target) when mechanotransduction is included as a potential modulator of inflammation. An overview of the analytical process is shown in Figure 4. Although far from clinical application, these results provide insight into novel characteristics of mechanotransduction and can guide more focussed experimental validation and exploration.

Among the numerous applications focussed on inflammation, we chose a series of studies on rheumatoid arthritis (RA) that presents in practice the versatility of the network approach delineated. The early Systems biology markup language network (or *map*) of rheumatoid arthritis (Wu et al., 2010) was built from lists of differentially expressed genes from microarrays, further interconnected using KEGG (Kanehisa et al., 2016). This work was the foundation of the rheumatoid arthritis map in the Disease Maps Project repository (Mazein et al., 2018), where Systems biology markup languages of other pathologies are collected. The final structure was analysed in the form of a network in a variety of ways: globally, tissue wise and module wise. This latter approach highlighted CRKL (CRK-like proto-oncogene) as a central node and a potential novel drug target. Its relevance was further explored with tools of dynamic simulation described in Section 4.2.

Finally, an extended, refined and actualised version of this same rheumatoid arthritis map was published at the beginning of the Covid-19 era (Singh et al., 2020). Despite a large amount of additional work, this shows how information from 10 years of research could be usefully embedded thanks to the use of systems biology markup language/systems biology graphical notation (SBML/SBGN) notation standards.

To conclude this section, we present applications of a widely used protein–protein interaction, built from a variety of sources including the Human Reference Interactome (Luck et al., 2020) and a variety of experimentally validated relationships derived from high-throughput yeast-two-hybrid and protein–protein co-complex interactions. This protein–protein interaction is presented here as a tool to repurpose drugs for pulmonary arterial hypertension (PAH) alone or as COVID-19 comorbidity (Wang & Loscalzo, 2021, 2023) and in Section 4.4 as the base to identify a relevant module (mathematically coherent set of molecules with a clinical characterisation) in type 2 diabetes.

The approach adopted here relies on mapping molecules of interest (pulmonary arterial hypertension disease genes and drugs direct or indirect targets) to the Human Interactome and then carefully analysing overlap and closeness among relevant modules, that is, tight groups of genes characterising a specific function or feature. This approach enabled the identification of specific drug target modules, within which several novel targets were identified. Importantly, the identification of specific modules allows for the isolation of molecular interactions that represent a mechanistic justification for drug repurposing. This represents a significant advantage of explainable network approaches over complex network representation learning (NLR, Section 4.3).

Further, this approach was used to identify drugs that could be used in COVID-19 patients with network representation learning comorbidity. The analysis extracts multiple molecular markers of each disease (proteins that are targets of SARS-CoV-2 and network representation learning markers) to define two disease modules and investigate different aspects of their similarity, using edge-based distances. Significant overlap among the structures that have been identified with network analysis (which can in general include target, markers,

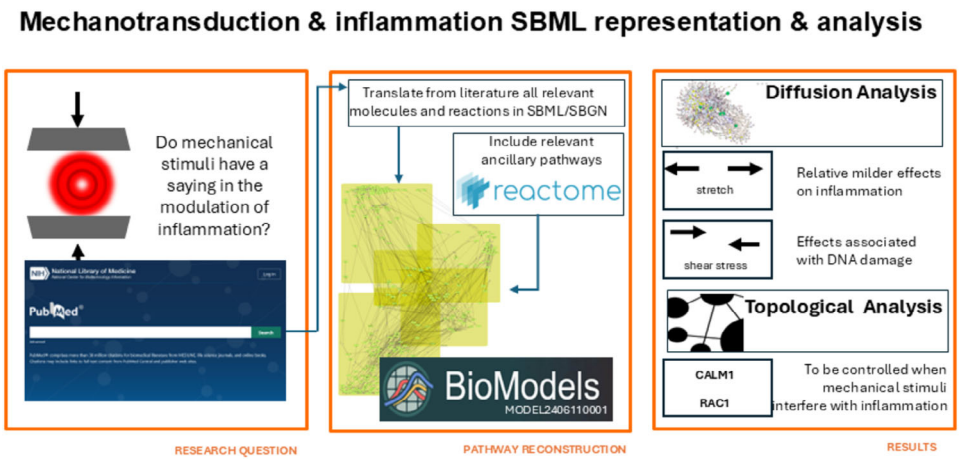

FIGURE 4 The methodological process starts from the formalisation of the research question, which translates into literature and pathway database query. The following step consists of the translation of the information scattered across the literature into the Systems biology markup language (SBML) formalism and then in the integration, where possible, with known corollary pathways. Finally, the pathway is released for public usage, improvement, check and expansion in Biomodels (Malik-Sheriff et al., 2020) and used as a base for network topological analysis. In particular, the analysis enables the identification of differential effects of mechanical stimuli, with stretch being less effective than other stimuli in impacting inflammation and with shear stress having the potential to interfere with DNA damage. Finally, comparison of this network with the inflammatory pathway alone, that is, when mechanotransduction is not considered integral part of the inflammatory pathway, allows identification of calmodulin1 (CALM1) and **Rac Family Small GTPase 1 (RAC1)** as a relevant target of mechanical forces (either harmful stress or therapy).

modules etc) suggests similarity between the diseases. For this reason, a second level of exploration was performed by mapping the differentially expressed genes in each disease, using both peripheral blood mononuclear cell (PBMC) and lung tissue RNA-seq data. Enrichment analysis revealed commonly triggered molecular functions (hypoxia, fibrosis, oxidative stress and immune response) and suggested potentially shared transcription factors, which were identified for each tissue (PBMC and lungs). Given these persisting pathobiological overlaps, the authors ultimately explored the similarities among each disease's drug targets: this final significant overlap suggested the investigation of 42 COVID-19 drugs in the case of network representation learning comorbidity. This network is also used in Section 4.4 where Topological Data Analysis (TDA) is applied.

4.1.1 | Considerations for applications to the transduction of physical stimuli

To begin with, transduction pathways should be represented using standard human/machine readable formats such as the SBML/Systems biology graphical notation formalisms. To date, only mechanotransduction has been reported in this way. Further, network analyses could easily identify overlap between different types of stimuli (mechanic, electric, magnetic and optic), by measuring distances and overlap between network modules and nodes. Enrichment analyses on these overlaps could highlight molecular functions benefiting from physical therapies and warn against harmful functions. Such functional overlap could also be used to identify equivalence or complementarity of physical therapies. The former could be used to offer alternatives to patients based on clinical conditions, accessibility of the area to be treated, pain conditions and more, the latter to suggest integrated therapies.

4.2 | Networks for dynamic simulations

Physical stimuli induce time-dependent biochemical interactions, which combined with other physiological and disease signals, and determine the abundance of the molecules involved in inflammatory responses. Network representation offers diverse techniques to replicate these dynamic processes (Mandel, 2004). In the following, we introduce Chemical Reaction Networks (CRNs) and Petri Nets (PNs), chosen for their ability to handle (upon integration with machine learning approaches) a relatively large number of entities (molecules). An introduction to the relevant theory is presented in Supporting Information.

Chemical reaction networks (Aris, 1965) describe the interactions between molecules. However, in this case, nodes do not represent individual molecules but all reactants and products of a reaction, and edges between two nodes represent the reaction. The effectiveness of these methods can be better understood through the following examples.

Craciun and colleagues (Craciun et al., 2006) studied reactions involving dihydrofolate reductase, an enzyme that promotes the production of tetrahydrofolate, which is crucial in the pathway for thymine synthesis, providing insight into the use of drugs like methotrexate that inhibit dihydrofolate reductase in chemotherapy treatments. The authors demonstrate that it is possible to predict the behaviour of tetrahydrofolate concentration in a controlled experiment solely based on mathematical principles derived from the CHEMICAL REACTION NETWORKS theory. In particular, it is feasible to predict the switch-like response mechanism of tetrahydrofolate concentration in reaction to minor fluctuations in the concentrations of the reagents, namely, dihydrofolate and NADPH. The prediction is confirmed by numerical simulations that replicate controlled experiments using experimental parameters: starting from low concentrations of dihydrofolate and NADPH and gradually increasing them, high concentrations of tetrahydrofolate are obtained until a threshold value of the reagents is reached, beyond which the concentration of the product drops drastically. By retracing the process backward and decreasing the amount of reagents, conversion into tetrahydrofolate remains inefficient until another switch-like process occurs, rapidly returning tetrahydrofolate concentrations to high levels. Switch-like responses are important nonlinear behaviours (a.k.a. *hysteresis cycles*) that explain abrupt changes in the response of a system to small increases of an input, followed by stable behaviour despite changes in the input, in this case the drug dosage. Chemical reaction networks models were also used to study the dynamics of several pathways involving the APC, KRAS, SMAD4 and TP53 genes, frequent driver mutations responsible for the development and progression of colorectal cancer (Sommariva et al., 2021). The network consisted of 419 proteins involved in 850 reactions, with all model parameters calibrated on literature data and the dynamics numerically solved via simplifications introduced by CHEMICAL REACTION NETWORKS theory. The authors also included both the effects of mutations on genes and inhibitory effects of Dabrafenib. This was accomplished by bringing the concentration of the protein associated with the mutated gene to zero and altering levels of the drug targets, respectively. The authors quantified the changes in the concentration of all the proteins involved in the network because of the mutations most frequently associated with colorectal cancer and then validated them with previously published data. Additionally, the authors obtained a detailed description of the action of Dabrafenib and identified an optimal drug dose capable of bringing the concentrations of the proteins close to the physiological state.

PNs (Petri & Reisig, 2008) are networks with a different structure (see also Figure S1); these are not characterised by nodes and edges but consist of two types of nodes, which in biological networks usually represent species (*places*) and chemical reactions (*transitions*). Dynamics are studied by letting *tokens* (virtual items that can represent gene expression, i.e. mRNAs, or other molecules carriers of biochemical signalling) flow among *places* via *transitions*.

The rheumatoid arthritis Systems Biology Markup Language (SBML) pathway described earlier (Wu et al., 2010) was analysed with Petri Network to explore the effect of a drug targeting CRKL on its neighbourhood. In one approach (Dent & Nardini, 2013), explicit conversion of Systems Biology Markup Language to signalling Petri

Network (SPN) was performed in a semi-automated way and identification of a reasonable number of *tokens* representing physiological, over- and under- expression were defined. Then it was determined how perturbations of CRKL protein (mostly down-regulation as the effect of a drug controlling the overexpression typical of rheumatoid arthritis) affected the rest of the network. By concentrating on the nodes whose *token* distribution was significantly changed before and after perturbation, the biological impact of such changes was assessed. Interestingly, this analysis highlighted the importance of **paxilline**, offering a mechanistic rationale to test tyrosine kinase inhibitors on rheumatoid arthritis (such as R406).

Trares and colleagues employed PNs to study the canonical and non-canonical pathways that connect **CD40 receptor** stimulation to the translocation of factor kappa-light-chain-enhancer (NF-kB) dimers into the nucleus (Trares et al., 2022). NF-kB activity plays a central role in both physiological and pathological processes: the canonical pathway mediates inflammatory responses, while the non-canonical pathway is involved in immune cell differentiation and maturation. Dysregulation of NF-kB is linked to severe diseases such as inflammatory bowel disease, rheumatoid arthritis and others. The authors generated two PNs: one for the canonical pathway and another for the non-canonical pathway, based on the literature. Additionally, a third Petri Network model that couples both pathways and their observed crosstalk was developed. A knockout analysis was conducted, systematically switching off each transition within the networks. The results identified which transitions have the greatest impact and closely corresponded to those reported in experimental perturbations, validating the models as tools for further analysis.

4.2.1 | Considerations for applications to the transduction of physical stimuli

Numerous applications for physical stimuli can be envisioned, once transduction pathways are drawn: Petri Network analysis can be used to simulate the differential effects of different stimuli, even of the same nature, for example as shown for mechanotransduction where *shear stress* and *stretch* appear to lead to slightly different effects. A similar approach could be adopted for optical stimuli of different wavelengths, and electrical stimuli and magnetic fields of different frequency. This type of information could be extended to pathological settings by integrating transduction and immune pathways with inflammatory disease maps. Importantly, once transductions have been characterised (for instance, for a given electrical frequency or type of mechanical stimulus), chemical reaction networks could be used to identify switch-like behaviours, offering support to testing ranges of dose–response curves for physical therapies, a highly underexplored area.

4.3 | Complex networks representation learning

Beyond the traditional network representation of node and edge sets, more recent and powerful network representations have been generated in the form of matrices (i.e. same-size vectors collectively arranged in rows or columns) and the identification of patterns discussed earlier in analyses on vectors. Vectors are derived from the network in a manner that optimises the extraction of all embedded information, including node attributes (characteristics beyond their relations to other nodes) and neighbourhood (nodes related to a node of interest). The benefit of this approach is the simplicity, both computationally and mathematically, of working with compact vectors instead of large-scale networks (e.g. neural networks [NN]). Working with vectors enables full exploitation of modern machine learning techniques, whether off the shelf or custom made. Such a paradigm is usually referred to as network representation learning (network representation learning) or network embedding. Here we mainly focus on network representation learning applications; more technical details can be found in the Supporting Information and Figure S2.

Importantly, while the results of network embedding have been proven much better than the ones obtained by statistical machine learning, especially on huge networks that could be otherwise intractable, it remains challenging to precisely control the effects of the embedding—specifically, the mechanics of encoding networks into vectors. This causes a lack of *explainability* in these approaches. Currently, efforts are underway to control this issue through the explainable artificial intelligence research area. Ethical, legal and social issues (ELSI) that surround artificial intelligence generally stem from this issue.

Among the earliest problems approached with this framework are link prediction and community detection, which represent the opportunity to identify missing network edges (i.e. biochemical connections) or more popular modules. In one paper (Yi et al., 2024), a user accessible platform (biochemical pathway prediction, BPP) was developed to exploit link prediction from a variety of representation learning models in the modelling of biological pathways. Importantly, BPP attempts to cope with explainable artificial intelligence by providing contributions of each participating element in the existing pathway as companion information.

Drug-target interaction prediction is among the most common applications in this area. Network representation learning can be used to embed the representations of both drugs and targets in the form of vectors in the network structure. Importantly, the vector representation contains information not only on the molecule but also on its network of interaction. When this representation is performed using different sources of information, then the vectors are extremely rich and all operations run on them carry along meaningful and complete information. Drug Artificial intelligence enables the representation of drug and target pairs, used then to predict drug-target activation and inhibition relationships (Zhang et al., 2023). Similarly, by learning from known drug-target interaction data, network representation learning can be applied to identify novel druggable targets that may be involved in disease mechanisms and can be targeted by small molecules (Liu et al., 2022).

Another interesting application is the use of Large Language Models (LLMs), based on a particular type of neural networks, to facilitate the creation of Systems Biology Markup Language (SBML)

pathways. In the field of bioinformatics and systems biology, these models are being leveraged to automate complex tasks, including the generation of kinetic models from natural language descriptions of biochemical reactions. For example, Kazuhiro Maeda and Hiroyuki Kurata (Maeda & Kurata, 2023) introduced KinModGPT, an innovative method that harnesses the power of Large language models to create Systems Biology Markup Language kinetic models from natural language descriptions. This approach, which combines GPT's language capabilities with a dedicated tool for biochemical modelling (Tellurium,(Choi et al., 2018), automates the conversion of natural language descriptions of complex biological processes into computable Systems Biology Markup Language models, accelerating model development and deepening our understanding of complex biological systems.

In addition, Large Language models have potential for enhancing network representation learning to learn more meaningful representations of biomedical molecules (Fan et al., 2024) and ease various prediction tasks on above-discussed biological network applications. For example, because there are rich textual descriptions of molecules, one can leverage Large Language Models to enhance text attributes of molecules and, together with graphic neural networks, conduct network representation learning to make downstream predictions.

4.3.1 | Considerations for applications to the transduction of physical stimuli

Large Language Models can support the core step of all approaches, which is the definition of transduction pathway, thereby easing lengthy manual reconstruction from the literature and enabling shorter cycles of repository updates. Such pathways could also take advantage of link prediction that could be very useful to complete the physical transduction pathways and to identify recurrent pathways (communities) among them. Finally, all drug-target prediction and drug repurposing approaches can be explored by replacing drug targets with physical therapies as the main actuators, or in reverse, to identify drugs that interfere with important nodes of transduction processes.

4.4 | Topological data analysis (TDA)

Topological data analysis (Edelsbrunner et al., 2000; Edelsbrunner & Harer, 2008) can characterise robust patterns, starting from a network structure in the form those described in Section 4.1. Networks can be presented in the intuitive form presented in Section 4.1 or as topological structures, where the focus is not on nodes connected by edges but on the items enclosed by edges (a.k.a. *holes*, see Supporting Information). Holes are objects used to characterise a network in topological data analysis and therefore, the number of holes and the 'shapes' of holes (depending on the dimension of the elements enclosing them) are a feature of the network. Specially, topological data analysis focusses on two main aspects regarding these topological features: (i) the number of each 'type' (a.k.a. dimension) of hole and (ii) their persistence, that is, for how long they can be detected during a process, called *filtration*, in which we incrementally retain (filter) network's elements as weight's values change. For instance, the co-expression value among genes (nodes) can be used to weight the edges. The weight is increased stepwise and for each step, a network is built, which includes the nodes connected by edges whose co-expression is below the current step value. Then, for each network in this step sequence, the number of holes is computed. With increasing values, new holes may appear and older holes may disappear. The larger the persistence of holes across steps, the more robust the hole and therefore its potential significance as a biomedical feature. In this framework, specialised mathematical tools can be exploited to extract and measure holes' characteristics' similarities.

The first example application of this approach involves the analysis of a protein–protein interaction network to detect meaningful targets/biomarkers. This application is particularly interesting as it enables the reuse of biological networks to extend information mining and identify additional/complementary robust patterns.

To perform topological data analysis, Benzekry and colleagues used a protein–protein interaction network converted from the KEGG, and built a weighted network by assigning to edges the minimum distance connecting two nodes in the original protein–protein interaction network (Benzekry et al., 2015). The authors found a negative correlation between the number of *holes* and the 5-year survival rate in treated cancer. Further, they studied changes in network hole patterns after removing individual or multiple proteins (nodes). They observed that molecules whose removal was associated with significant drops in the number of holes corresponded to targets for better-performing therapies. For instance, removal of RAS family proteins, a well-known set of oncogene proteins, caused drops in the number of holes in protein–protein interaction networks for acute myeloblastic leukaemia, glioma, and bladder and thyroid cancers.

Another study (Song, 2023) applied topological data analysis on the protein–protein interaction discussed in Section 4.1 (Wang & Loscalzo, 2021). In this application, Genome-Wide Association Study (GWAS) hits for type 2 diabetes (T2D) were mapped on the protein–protein interaction using the same GWAS hit *P*-values, ranging from 0 to 5×10^{-8} as weights. The objective was to identify the so-called *observable disease module*, a large and stable cluster with clinic-phenotypic relevance. Given the incompleteness of GWAS studies and of protein–protein interaction reconstruction, structures that were insensitive to weight value changes were identified, and the most robust were joined into a proxy of this *observable disease module*. This cluster indeed appears to be significant when compared to random rewiring of the protein–protein interaction. In particular, the nodes that were part of the most stable structures identified sets of genes enriched for **mTOR**, forkhead box class O (FoxO), AMPK and **PI3K-Akt** signalling, known as a longevity and transcriptional dysregulation pathway in cancer and related to type 2 diabetes. Therefore, this approach is an alternative to the identification of modules and communities mentioned in Sections 4.1 and 4.3. Importantly, the topological data analysis approach is characterised by robustness and explainability, as it is a theoretically based mathematical approach.

Interestingly, several methodologies have been developed to build a topological network starting not only from networks but also including point clouds (set of points described by their coordinates in the space), images and time series. These approaches hold great potential for applications in drug repurposing. Here, we describe an example where topological data analysis has been used to identify drug candidates for the treatment of COVID-19 patients at the early stage of disease spread starting from point cloud data (Pérez-Moraga et al., 2021). The objective was to describe a protein as a network, based on its atomic structure: each atom represents a node and the edge their distance (if two atoms have distance 0.9 Å, we assign 0.9 to the edge linking them). Networks were constructed for each SARS-CoV-2-involved protein and for each protein in the Protein Data Bank (PDB, Berman et al., 2000) that is a target for an FDA approved drug. Next, the filtration patterns for each protein are observed and it is assumed that similar patterns identify similar proteins. In this way, Protein Data Bank proteins could be chosen as potential drug targets, based on their structural similarity to SARS-CoV-2-involved proteins, and the related drugs as candidates for treatment of COVID-19 patients. The investigators identified 16 compounds related to three SARS-CoV-2 proteins, three of which have been positively evaluated for their effectivity and safeness in clinical trials (indomethacin, dexamethasone and spironolactone).

4.4.1 | Considerations for applications to the transduction of physical stimuli

Transposing these procedures to the study of physical stimuli in inflammation, one can consider a network involving different biological pathways implicated in inflammation (see the idea of a greater inflammatory pathway by Maturo et al., 2020) enriched with the effects of physical stimuli. One can then envision studying how removal of pathway members affects network topology to identify meaningful targets within the system.

Similarly, this approach could be used to test how holes and their characteristics change with different types of transductions, or the robustness of certain effects, by removing central nodes. It is also possible to assign weights to each node or edge describing relevant chemical/physical properties and that are sensitive to physical stimuli (pH, isoelectric point) to assess how the structure of the network changes accordingly, and up to which values of such parameters the network remains stable.

5 | CONCLUSIONS

We reviewed the existing knowledge on the impact of physical stimuli on inflammatory pathways at the molecular and cellular level (Sections 2.1–2.4). The level of understanding for each stimulus is heterogeneous and biological mechanisms, when available, are confined to the biological realm in which they were generated. To the best of our knowledge, our effort (Section 2) to describe overlapping mechanisms is a unique contribution. Unfortunately, the partial information available prevents a complete understanding of the potential and limitations of physical stimuli as anti-inflammatory therapies, given that studies to date have focussed on a limited and varied set of effectors and fail to account for the complexity of molecular interactions. Importantly, no general consensus pathway capable of explaining transduction mechanisms, the interactions among them, and with the innate immune response has yet been defined.

Integrating the partial information available is facilitated by the powerful tools of network-based theories. Physical stimuli likely influence immunity at least in part via cytokines and ion channels. However, whether the latter are the most effective targets (more stable features), or whether subtle changes in other elements of the pathway biochemistry (network parameters) would be more effective targets or marker, is a matter that requires more study to be elucidated.

Networks are widely used and effective tools to overcome fragmentation. In their most intuitive form, nodes are biochemical items and edges are reactions. Such networks can easily represent very large and complex biochemical associations. When these networks attempt to model diseases, they are often referred to as *maps*, and when their representation is the starting point for more advanced mathematical or computational modelling, they are often named *graphs*. From this intuitive and yet powerful representation, other advanced graph-based approaches can be exploited to advance knowledge. We presented a rich, although non-exhaustive, set of graph-based methodologies focussing on examples that could be translated to physical stimuli. We then presented a limited set of possible practical applications; depending on the question under study, many more options can be designed.

In this review, we highlighted a number of potential future directions, which we briefly summarise here, as a potential roadmap to better understand the impact of physical stimuli on inflammatory pathways:

- Definition of physical transduction pathways, using both manual curation from literature and Large Language Models for automated approaches, in standard human and machine readable (SBML/Systems biology graphical notation) format. The most likely solution will be integration of both approaches to guarantee that the power of automated pathways production is backed by expert curation, so called *human-in-the-loop*, to guarantee explainability, that is, trustability of the reconstructed pathways.
- Usage of network representation learning link prediction capabilities to recommend completion of transduction pathways, by suggesting missing edges/links in the pathways, particularly in their overlooked interaction with inflammation.
- Highlight downstream and systemic effects of different physical stimuli, at different wavelengths, and electrical stimuli and magnetic fields of different frequency with Petri Network simulations.
- Introduce information on stimuli sensitive variables (pH, isoelectric point) in physical transduction pathways as edge weights and explore via topological data analysis for values at which the network preserves its topology correlated to physiological conditions.

- Within the earlier identified ranges of physiological operation, identification of switch-like behaviours with chemical reaction networks, providing a basis for testing ranges of dose–response curves for physical therapies, this is a highly underexplored area.
- Identification of overlap among physical transductions of different nature in the form of modules/community using network representation learning community detection methods and measures of similarity in static network analyses, respectively. Molecular functional enrichment analyses on these modules/communities could highlight biological functions benefiting from physical therapies and highlight potentially damaging functions. Further, such functional overlaps could be the basis for identifying equivalence or complementarity among physical therapies. For example, based on availability, individual preferences and disease conditions, one could explore how the effects of an optical stimulus delivered at certain wavelength can be replaced by electro-stimuli at a precise frequency in alternating current.
- Integrate physical transduction pathways into disease maps and identify overlapping modules and distances; extract topologically relevant nodes to assess their importance and compare them to drug targets to assess drug-physical therapies synergies. Exploit this information in drug-target prediction frameworks.

We propose that such research would improve the perception of physical therapies, which have been long neglected, and studied and disseminated in a highly heterogeneous manner (C. Nardini et al., 2022). We posit that employing state-of-the-art network medicine methodologies will provide an important bridge to better understand the impact of physical stimuli on inflammation. Finally, we hope that our work will spark curiosity in the anti-inflammatory potential of physical stimuli, for the ultimate benefit of patients.

5.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2023/24 (Alexander, Christopoulos, Davenport, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, et al., 2023; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, Annett, et al., 2023; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, Beuve, et al., 2023; Alexander, Mathie, Peters, Veale, Striessnig, Kelly, Armstrong, Faccenda, Harding, Davies, Aldrich, et al., 2023).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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N/A-Review.

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