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TRANSDERMAL NANOEMULGEL OF AN ANTI-INFLAMMATORY PHYTOCONSTITUENT FOR OSTEOARTHRITIS: AN IN SILICO FORMULATION-DESIGN AND MOLECULAR TARGET STUDY

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ABSTRACT

Background: Osteoarthritis is the most prevalent joint disease worldwide and its management still depends heavily on oral non-steroidal anti-inflammatory drugs, whose gastrointestinal and cardiovascular risks limit long-term use. Boswellic acids, the pentacyclic triterpenic acids of Boswellia serrata, inhibit the 5-lipoxygenase pathway and other inflammatory mediators central to osteoarthritis, but their extreme lipophilicity and poor oral bioavailability restrict clinical translation. A transdermal nanoemulgel is a rational way to deliver such a molecule to a superficial joint while bypassing first-pass metabolism. **Objective:** To profile the five principal boswellic acid congeners computationally, to predict their suitability for transdermal delivery, to test whether their molecular targets are over-represented among osteoarthritis-associated genes, and to translate the resulting property profile into a defensible nanoemulgel formulation-design rationale. **Methods:** Physicochemical descriptors and drug-likeness were calculated in RDKit for the five boswellic acids and two reference topical non-steroidal anti-inflammatory drugs. The steady-state skin permeability coefficient was predicted with the Potts-Guy model. Literature-compiled boswellic acid targets were intersected with an osteoarthritis gene set and the overlap tested by the hypergeometric distribution. All results are computational predictions; no experimental determination was performed. **Results:** The boswellic acids were compact, rigid and highly lipophilic (calculated logP 6.41 to 7.80, topological polar surface area 57.53 to 80.67 square angstrom, one to two rotatable bonds). Predicted log Kp values ranged from -1.02 to -0.20 cm/h, higher than diclofenac (-1.41) and ibuprofen (-1.78), a level of favourable intrinsic stratum-corneum permeability that is offset by very low aqueous solubility. Sixteen predicted targets intersected the osteoarthritis gene set in twelve genes, a 405-fold enrichment over chance (hypergeometric p = 3.94 x 10^-31), with 5-lipoxygenase the most connected node. **Conclusion:** The computed profile supports a solubilising lipid nanoemulgel as a mechanistically justified transdermal strategy for boswellic acids in osteoarthritis, and identifies the specific compound and targets that bench validation should address.

Keywords: boswellic acid; osteoarthritis; nanoemulgel; transdermal delivery; molecular target analysis; skin permeability; in silico.

1. Introduction

Osteoarthritis is the commonest form of arthritis and a leading cause of disability in older adults. The Global Burden of Disease Study 2021 estimated that osteoarthritis affected close to 600 million people worldwide in 2020, with the burden projected to keep rising as populations age and obesity becomes more common [1]. The knee is the most frequently affected joint, and because osteoarthritis is superficial at the knee and the small joints of the hand, the affected cartilage and synovium lie within reach of a drug applied to the overlying skin.

For most of its history osteoarthritis was described as a purely mechanical, degenerative process. That view has been replaced by an understanding of the disease as a low-grade inflammatory condition in which the cartilage, subchondral bone and synovium interact through a network of cytokines and enzymes [3]. Interleukin-1 beta and tumour necrosis factor alpha drive chondrocytes to produce matrix-degrading enzymes, of which matrix metalloproteinase-13 is the principal collagenase responsible for the irreversible loss of type II collagen [4]. The same cytokines activate nuclear factor kappa B and the arachidonic acid cascade, which raises the local concentrations of prostaglandin E2 and leukotrienes and sustains the pain and swelling that bring patients to the clinic [3]. This inflammatory reframing matters for therapy, because it identifies specific molecular mediators that a small molecule might modulate.

Current pharmacological management reflects both the mechanism and its limits. International guidelines place topical and oral non-steroidal anti-inflammatory drugs at the centre of symptomatic treatment, and specifically recommend topical agents for knee osteoarthritis because they achieve local concentrations while limiting systemic exposure [2]. Oral non-steroidal anti-inflammatory drugs, though effective, carry well-recognised gastrointestinal, renal and cardiovascular risks that make them unsuitable for the prolonged, often lifelong, use that osteoarthritis demands [2]. There is therefore a clear place for a locally acting, anti-inflammatory agent with a mechanism complementary to cyclo-oxygenase inhibition and a safety profile that supports long-term application.

The transdermal route is attractive for osteoarthritis for reasons that are anatomical as much as pharmacological. The joints most often affected, the knee and the interphalangeal joints, lie close beneath the skin, and a drug applied over them can reach the synovium and superficial cartilage by direct diffusion through the tissue as well as by the systemic circulation, so that the target concentration is achieved with a fraction of the systemic exposure an oral dose would require. Delivery through the skin also bypasses the hepatic first-pass metabolism that degrades many orally administered agents, maintains steadier concentrations than the peaks and troughs of oral dosing, and can be stopped simply by removing the preparation, which is a practical advantage for a chronic condition managed by the patient at home. For a molecule that additionally inhibits the leukotriene

pathway, a transdermal preparation offers something the marketed topical non-steroidal anti-inflammatory drugs do not, namely local suppression of a mediator arm that cyclo-oxygenase inhibition leaves untouched.

Boswellic acids answer that description. They are the pentacyclic triterpenic acids of the oleogum resin of *Boswellia serrata*, a plant used for inflammatory complaints across centuries of traditional practice. The most studied congeners are alpha-boswellic acid, beta-boswellic acid, 11-keto-beta-boswellic acid and 3-O-acetyl-11-keto-beta-boswellic acid, the last of these, abbreviated AKBA, is the most pharmacologically active. Their signature mechanism is inhibition of 5-lipoxygenase, the enzyme that initiates leukotriene synthesis, and this action is direct and non-redox, a mechanism that sets boswellic acids apart from conventional lipoxygenase inhibitors [5,7]. Beyond 5-lipoxygenase, boswellic acids inhibit microsomal prostaglandin E synthase-1, human leukocyte elastase, cathepsin G and the nuclear factor kappa B signalling axis, so that they present a multi-target anti-inflammatory profile that maps onto several of the mediators active in osteoarthritis [6,9]. Randomised trials and a systematic review with meta-analysis have reported that *Boswellia* extracts reduce pain and stiffness and improve joint function in knee osteoarthritis, which supports the biological relevance of the chemistry [8].

The obstacle is delivery. Boswellic acids are large, rigid and extremely lipophilic, and their oral bioavailability is low: 11-keto-beta-boswellic acid binds plasma albumin almost completely and reaches only modest systemic concentrations, which is why oral dosing has struggled to suppress leukotriene synthesis in patients despite clear activity in vitro [10]. These same properties, however, are not uniformly unfavourable. High lipophilicity and low polar surface area favour partitioning into the lipid-rich stratum corneum, so the molecule that resists oral absorption may be well suited to the transdermal route, provided the formulation overcomes its poor aqueous solubility. A nanoemulgel, a nanoemulsion immobilised in a hydrogel, is a delivery system designed for exactly this situation: it solubilises a lipophilic drug in a nanoscale oil phase, presents it at high thermodynamic activity to the skin surface, and gives the semisolid consistency needed for topical application [11,12].

This study approaches the formulation question computationally, before any bench work. The objectives were fourfold: to characterise the physicochemical and drug-likeness profile of the five principal boswellic acid congeners; to predict their skin permeability and benchmark it against marketed topical non-steroidal anti-inflammatory drugs; to test whether the molecular targets of boswellic acids are statistically over-represented among osteoarthritis-associated genes rather than merely plausible; and to translate the resulting profile into a rational nanoemulgel design. All findings reported here are computational predictions generated in silico, intended to prioritise and

justify subsequent laboratory formulation and testing rather than to replace it.

2. Materials and Methods

2.1 Compounds and structure preparation

Five boswellic acid congeners were studied: alpha-boswellic acid, beta-boswellic acid, 11-keto-beta-boswellic acid, 3-O-acetyl-beta-boswellic acid and 3-O-acetyl-11-keto-beta-boswellic acid (AKBA). Two marketed topical non-steroidal anti-inflammatory drugs, diclofenac and ibuprofen, were included as permeability benchmarks. Each structure was represented as a SMILES string and verified before use by confirming that the molecular formula and molecular weight computed by the toolkit matched the published values for the compound, so that a transcription error could not propagate into the descriptors. Structures were standardised in RDKit (version 2026.03.4) by retaining the largest covalent fragment and regenerating the canonical form.

2.2 Physicochemical and drug-likeness profiling

For every compound the following were calculated in RDKit: molecular weight, calculated octanol-water partition coefficient by the Crippen method, topological polar surface area, hydrogen-bond donor and acceptor counts, rotatable-bond count, aromatic ring count, fraction of sp3-hybridised carbons, molar refractivity and the quantitative estimate of drug-likeness. Compliance with oral drug-likeness was assessed against the Lipinski rule of five [15] and the Veber, Egan and Ghose filters, the number of violations of each rule set being recorded. This physicochemical and drug-likeness workflow follows the approach implemented in established web tools for in silico absorption, distribution, metabolism and excretion prediction [13]. All values are calculated properties; none were measured.

2.3 Skin permeability prediction

The steady-state skin permeability coefficient of each compound was predicted from its calculated logP and molecular weight using the Potts-Guy quantitative structure-permeability relationship, log Kp = -2.7 + 0.71(cLogP) - 0.0061(MW), where Kp is expressed in cm/h [14]. The predicted coefficients of the boswellic acids were compared with those of the two reference drugs. log Kp is a model prediction from lipophilicity and size alone; it does not represent a measured flux and does not account for the vehicle, penetration enhancers or the thermodynamic activity of the drug in a given formulation.

2.4 Molecular target analysis

Molecular targets of boswellic acids were compiled from the primary and review literature on their pharmacology, namely the accounts of Poeckel and Werz, Ammon, and Roy and colleagues [5,6,9], and expressed as official human gene symbols. A compound-target edge list was assembled in which each congener was linked to the targets reported for it, to give 37 unique compound-target pairs across the five congeners and 16 distinct targets. An osteoarthritis-associated gene set was compiled from the reviews of Molnar and colleagues on the

cytokines and chemokines of osteoarthritis and of Hu and Ecker on matrix metalloproteinase-13, yielding 37 genes [3,4]. The two sets were intersected, and the statistical significance of the overlap was assessed with the hypergeometric distribution against a background of 20000 protein-coding genes, giving the expected overlap, the fold enrichment and the exact probability. Within the shared set, each target was scored by the number of congeners annotated to it, giving a connectivity ranking. The edges and gene labels are imported annotations from the cited sources; the intersection sizes, the fold enrichment, the hypergeometric probability and the connectivity ranks are the computed results.

2.5 Software and reproducibility

All analyses were carried out in Python 3.11 using RDKit 2026.03.4, NumPy, pandas, SciPy and NetworkX. Every reported value was recorded at run time together with the tool, version, parameters and inputs that produced it. The analysis scripts and the machine-readable run record are available as described under Data availability.

3. Results

3.1 Physicochemical profile and drug-likeness

The calculated physicochemical properties of the five boswellic acids and the two reference drugs are given in Table 1, and the structures of the congeners are shown in Figure 1.

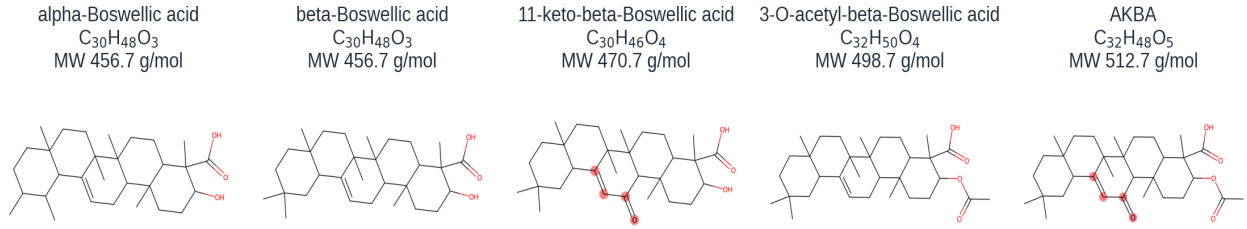

Figure 1. Two-dimensional structures of the five boswellic acid congeners studied, with molecular formula and molecular weight beneath each.

The boswellic acids form a tight chemical cluster distinct from the reference non-steroidal anti-inflammatory drugs. Their molecular weights ranged from 456.71 g/mol for alpha- and beta-boswellic acid to 512.73 g/mol for AKBA, all substantially larger than diclofenac (296.15) and ibuprofen (206.28). They were markedly more lipophilic, with calculated logP values between 6.41 for 11-keto-beta-boswellic acid and 7.80 for 3-O-acetyl-beta-boswellic acid, compared with 4.36 and 3.07 for the reference drugs. Despite this size and lipophilicity the congeners were compact and rigid: topological polar surface area lay between 57.53 and 80.67 square angstrom, well below the 140 square angstrom threshold associated with poor permeation, and each carried only one or two rotatable bonds and no aromatic rings, with a fraction of sp3 carbons of 0.84 or above.

The consequences for oral drug-likeness are visible in the violation counts. Every boswellic

acid breached at least one Lipinski criterion, in all cases the calculated logP exceeding 5, and AKBA additionally exceeded the 500 g/mol weight limit, so it carries two violations. None of the congeners violated the Veber rotatable-bond or polar-surface-area limits, and their quantitative estimate of drug-likeness values, between 0.31 and 0.46, were well below those of diclofenac (0.88) and ibuprofen (0.82). The picture is internally consistent: these are lipophilic triterpenoids that sit outside conventional oral drug space chiefly because of their lipophilicity and size, not because of polarity or flexibility.

The chemical modifications that distinguish the congeners map cleanly onto the descriptors and explain the spread within the series. Introduction of the 11-keto group, which converts beta-boswellic acid to 11-keto-beta-boswellic acid, adds a hydrogen-bond acceptor and raises topological polar surface area from 57.53 to 74.60 square angstrom while lowering calculated logP from 7.23 to 6.41, because the carbonyl is polar. Acetylation of the 3-hydroxyl has the opposite effect on hydrogen bonding: it removes a donor and raises calculated logP, so that 3-O-acetyl-beta-boswellic acid is the most lipophilic member at 7.80. AKBA combines both modifications and therefore carries the highest acceptor count and the largest polar surface area of the series, 80.67 square angstrom, together with the highest molecular weight. These are small differences on an absolute scale, and all five congeners remain firmly in the compact, rigid, lipophilic region of chemical space, but they are the differences that determine the predicted permeability ranking in the next section.

Table 1. Calculated physicochemical properties and Lipinski compliance of the five boswellic acid congeners and two reference topical non-steroidal anti-inflammatory drugs.

Compound	MW	cLogP	TPSA	HBD	HBA	RotB	FCsp3	QED	Lipinski viol.
alpha-Boswellic acid	456.71	7.09	57.53	2	2	1	0.90	0.41	1
beta-Boswellic acid	456.71	7.23	57.53	2	2	1	0.90	0.41	1
11-keto-beta-Boswellic acid	470.69	6.41	74.60	2	3	1	0.87	0.46	1
3-O-acetyl-beta-Boswellic acid	498.75	7.80	63.60	1	3	2	0.88	0.31	1
AKBA	512.73	6.98	80.67	1	4	2	0.84	0.40	2
Diclofenac	296.15	4.36	49.33	2	2	4	0.07	0.88	0
Ibuprofen	206.28	3.07	37.30	1	1	4	0.46	0.82	0

3.2 Predicted skin permeability

The predicted steady-state skin permeability coefficients are given in Table 2 and shown in Figure 2b. Every boswellic acid was predicted to permeate the stratum corneum more readily than either reference drug. Predicted log Kp values ranged from -1.02 cm/h for 11-keto-beta-boswellic acid to -0.20 cm/h for 3-O-acetyl-beta-boswellic acid, with AKBA at -0.87. Both reference drugs, which are formulated as marketed topical products, had lower predicted coefficients, diclofenac at -1.41 and ibuprofen at

-1.78. Because the Potts-Guy coefficient rises with lipophilicity, the high calculated logP of the boswellic acids drives their high predicted permeability, and the acetylated congeners, being the most lipophilic, are predicted to permeate best while the keto congeners, being less lipophilic, permeate least within the series.

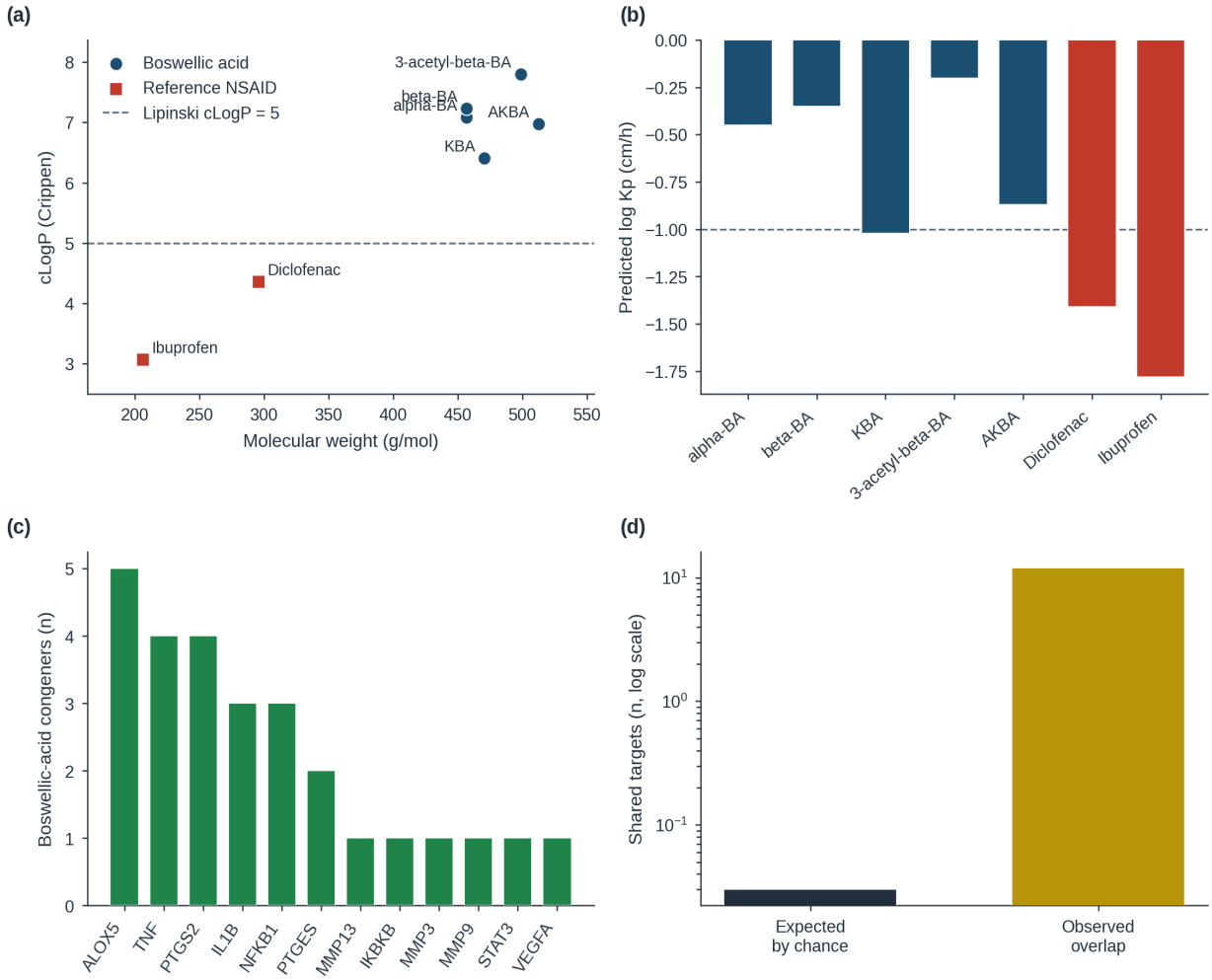

Figure 2. Computational profile of the boswellic acids. (a) Calculated logP against molecular weight for the five congeners (circles) and the two reference topical non-steroidal anti-inflammatory drugs (squares); the dashed line marks the Lipinski calculated logP limit of 5. (b) Predicted steady-state skin permeability coefficient (log Kp, cm/h) from the Potts-Guy model, with a reference line at log Kp = -1; boswellic acids in blue, reference drugs in red. (c) Connectivity of each shared target, scored as the number of boswellic acid congeners annotated to it. (d) Observed overlap between predicted boswellic acid targets and osteoarthritis genes (twelve genes) against the overlap expected by chance (0.03 genes), on a logarithmic scale. All plotted values are computational predictions.

Table 2. Predicted steady-state skin permeability coefficient (log Kp) of each compound from the Potts-Guy model, log Kp = -2.7 + 0.71(cLogP) - 0.0061(MW), with Kp in cm/h.

Compound	MW	cLogP	log Kp (cm/h)
alpha-Boswellic acid	456.71	7.09	-0.45
beta-Boswellic acid	456.71	7.23	-0.35
11-keto-beta-Boswellic acid	470.69	6.41	-1.02
3-O-acetyl-beta-Boswellic acid	498.75	7.80	-0.20
AKBA	512.73	6.98	-0.87
Diclofenac	296.15	4.36	-1.41
Ibuprofen	206.28	3.07	-1.78

3.3 Over-representation of boswellic acid targets among osteoarthritis genes

The 16 predicted boswellic acid targets were intersected with the 37 osteoarthritis-associated genes. Twelve genes were shared: ALOX5, IKBKB, IL1B, MMP13, MMP3, MMP9, NFKB1, PTGES, PTGS2, STAT3, TNF and VEGFA. Against a background of 20000 protein-coding genes the overlap expected by chance was 0.03 genes, so an observed overlap of twelve represents a 405-fold enrichment, and the probability of an intersection this large arising by chance was 3.94 x 10^-31 by the hypergeometric test. The observed and chance-expected overlaps are contrasted in Figure 2d. The shared genes are not peripheral to osteoarthritis: they include the interleukin-1 beta and tumour necrosis factor cytokines that drive the disease, the nuclear factor kappa B pathway components that transduce their signal, the prostaglandin and leukotriene enzymes PTGS2, PTGES and ALOX5, and the matrix metalloproteinases MMP3, MMP9 and MMP13 responsible for cartilage breakdown.

The connectivity of each shared target across the congener series is shown in Figure 2c. 5-lipoxygenase, encoded by ALOX5, was the most connected target, annotated to all five congeners, consistent with its position as the defining boswellic acid target. Tumour necrosis factor and cyclo-oxygenase-2 (PTGS2) followed, each linked to four congeners, then interleukin-1 beta and the nuclear factor kappa B subunit NFKB1, each linked to three, and microsomal prostaglandin E synthase-1 (PTGES) to two. The remaining shared targets, including MMP13, were each annotated to a single congener in the compiled set. The ranking places the leukotriene and prostaglandin machinery, together with the nuclear factor kappa B axis, at the centre of the predicted mechanism, with the matrix metalloproteinases as downstream effectors that fewer of the individual congeners have been reported to reach directly.

3.4 Formulation-design rationale

The computed profile points consistently toward one class of transdermal delivery system. The favourable predicted permeability of the boswellic acids reflects their affinity for the stratum corneum, but their very high logP and correspondingly low aqueous solubility mean that in a simple aqueous or hydroalcoholic vehicle the dissolved drug concentration, and therefore the thermodynamic activity that drives permeation, would be low. The rational response is a vehicle that solubilises the drug in a lipid

phase and presents it at high activity, which is the defining feature of a nanoemulsion. Immobilising that nanoemulsion in a hydrophilic gel matrix converts a mobile, cosmetically unappealing liquid into a spreadable semisolid suitable for application over a joint, without sacrificing the nanoscale droplet size that keeps the drug solubilised and increases the surface area available for partitioning [11,12].

The design that follows from the descriptors is therefore a nanoemulgel in which the boswellic acid fraction, most usefully an AKBA-enriched *Boswellia serrata* extract, is dissolved in an oil phase chosen for high triterpenoid solubility, emulsified with a surfactant and cosurfactant combination whose blend is matched to the low required hydrophilic-lipophilic balance of that lipophilic oil, and the resulting nanoemulsion incorporated into a carbomer or comparable hydrogel. The compact, low-polar-surface-area, low-rotatable-bond character of the drug supports partitioning once solubilised, and the acetylated congeners, which the model ranks as the most permeable, argue for an extract or a semisynthetic fraction enriched in the acetyl-boswellic acids rather than the free keto acids. Comparable boswellic acid and lipid nanocarrier systems have achieved nanometric droplet sizes and enhanced skin permeation experimentally, which sets the performance range that a laboratory realisation of this design should aim to reproduce and confirm [11,12].

4. Discussion

The central finding of this study is that the very properties that make boswellic acids poor oral drugs make them promising candidates for transdermal delivery, and that their molecular targets coincide, to a degree far beyond chance, with the mediators that drive osteoarthritis. Each of these observations is a computational prediction, and each carries a specific and testable implication for the formulation scientist.

The physicochemical analysis reconciles two facts that at first appear to conflict: boswellic acids are active anti-inflammatory molecules, yet oral dosing achieves disappointing systemic exposure [10]. The calculated profile locates the problem precisely in lipophilicity and size rather than in polarity or conformational flexibility. With calculated logP values above 6 and, for AKBA, a molecular weight above 500 g/mol, these compounds violate the Lipinski limits that predict poor oral absorption, and their low quantitative drug-likeness scores place them well outside conventional oral drug space [15]. The same lipophilicity, combined with a topological polar surface area far below the permeation threshold and a rigid, compact skeleton, is the property set that favours passage into the lipid lamellae of the stratum corneum. The transdermal route does not fight the chemistry of the molecule, it exploits it.

The permeability prediction sharpens this argument but also marks its limit. The Potts-Guy model predicts higher stratum-corneum permeability coefficients for every boswellic acid than for diclofenac or ibuprofen, both of

which are successfully marketed as topical products, which is an encouraging benchmark for the intrinsic permeability of the triterpenoids. The prediction must be read with care, however. The Potts-Guy relationship is derived largely from moderately lipophilic permeants and is known to overestimate the permeability coefficient of very lipophilic molecules, because at high logP the rate-limiting step shifts from diffusion through the stratum corneum to partitioning out of it into the more aqueous viable epidermis, and because the maximum achievable flux becomes limited by the drug's low aqueous solubility rather than by its permeability coefficient. The high predicted log Kp of the boswellic acids should therefore be interpreted as favourable intrinsic barrier permeability that will be realised as useful flux only if the formulation supplies the drug at sufficient thermodynamic activity. This is the quantitative core of the case for a solubilising nanoemulgel rather than a simple gel, and it converts a general preference for nanocarriers into a specific, mechanism-based design requirement. The route from this molecule to a joint, and the delivery system that serves it, are summarised in Figure 3.

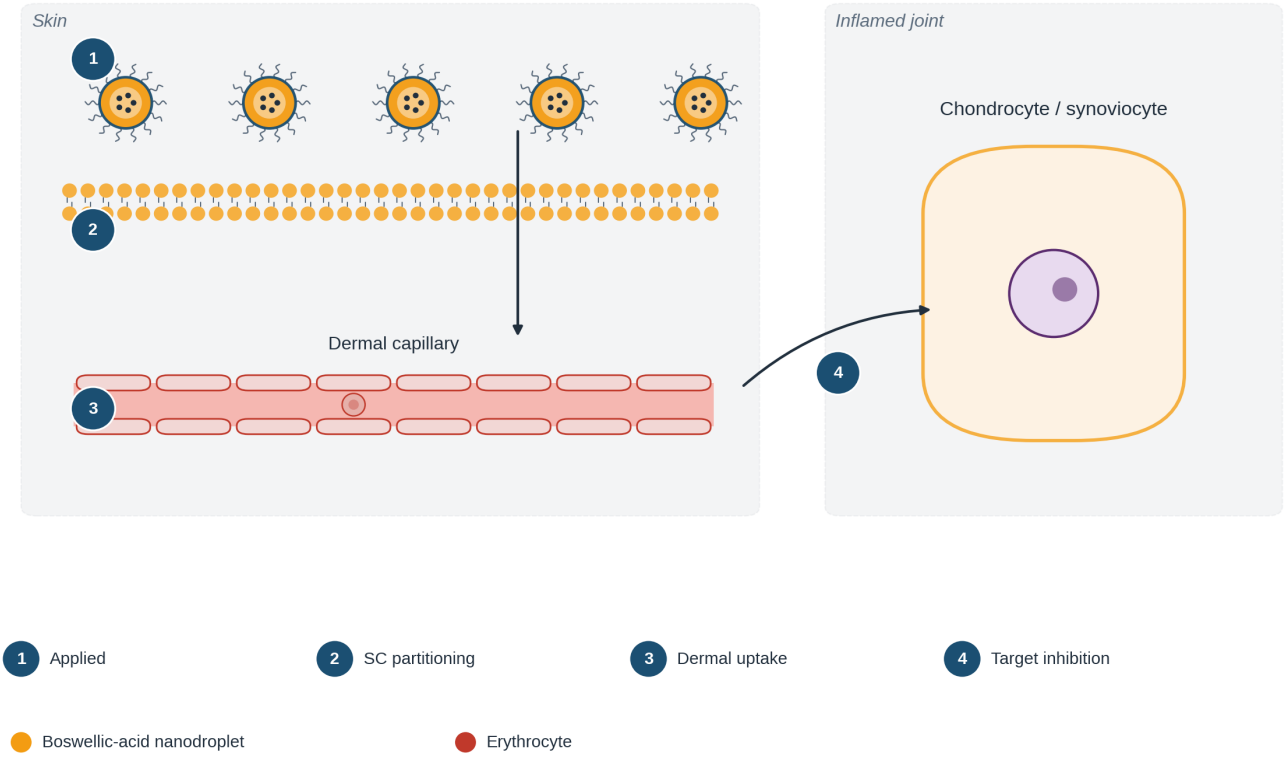

Figure 3. Schematic of the proposed transdermal route and molecular targets. A boswellic acid nanoemulgel applied to the skin over an affected joint (step 1) solubilises the lipophilic drug in nanoscale droplets that partition into the stratum corneum (step 2) and reach the dermal microcirculation and underlying tissue (step 3), where the drug inhibits 5-lipoxygenase, microsomal prostaglandin E synthase-1 and the nuclear factor kappa B axis in chondrocytes and synoviocytes of the inflamed joint (step 4).

The target analysis moves the argument from delivery to mechanism. That boswellic acids act on inflammatory pathways is established [5,6,9]; what the overlap test adds is a quantitative statement that their targets are specifically, not incidentally, the targets of osteoarthritis. A 405-fold enrichment and a hypergeometric probability of 3.94 x 10^-31 are strong by any statistical standard, and the identity of the shared genes is biologically coherent: the leukotriene and prostaglandin enzymes ALOX5, PTGES and PTGS2, the cytokines IL1B and TNF, the nuclear factor kappa B components, and the collagen- and matrix-degrading metalloproteinases MMP3, MMP9 and MMP13 that execute cartilage loss [3,4]. The connectivity ranking, placing 5-lipoxygenase at the centre with the cytokine and nuclear factor kappa B machinery around it, recovers the known pharmacology of boswellic acids from an independent direction and identifies AKBA, which reaches the widest set of these targets, as the congener on which formulation and testing should concentrate.

The predicted permeability ranking is consistent with the direction of the experimental nanocarrier literature, which is a useful external check on a model prediction. AKBA formulated in nanostructured lipid carriers has been reported to permeate skin substantially better than a plain gel of the same drug, confirming both that the free triterpenoid is permeation-limited in a simple vehicle and that a lipid nanocarrier relieves that limitation [11]. Nanoemulgels of other poorly soluble anti-inflammatory acids, such as diflunisal, have likewise shown enhanced topical delivery and anti-inflammatory effect relative to conventional formulations [12]. The present analysis does not reproduce those flux measurements, and could not, but it explains them: a molecule whose predicted permeability coefficient is high yet whose flux from a simple vehicle is low is precisely a molecule that a solubilising nanoscale oil phase should help, and the descriptor profile identifies the boswellic acids as members of that class. The convergence of an independent computational prediction with the reported behaviour of real formulations strengthens the case for the design proposed here.

The mechanistic reading of the target analysis is worth drawing out, because it bears on why a boswellic acid preparation would add to, rather than duplicate, current topical therapy. Marketed topical non-steroidal anti-inflammatory drugs act almost entirely through cyclo-oxygenase, reducing prostaglandin synthesis while leaving the parallel 5-lipoxygenase branch of the arachidonic acid cascade intact. Boswellic acids inhibit 5-lipoxygenase directly, and the connectivity analysis recovered ALOX5 as the target common to all five congeners, so a boswellic acid nanoemulgel would suppress leukotriene formation in the joint, a mediator arm implicated in the synovial inflammation of osteoarthritis and untouched by cyclo-oxygenase inhibitors [5,7]. The shared-target set further indicates action on microsomal prostaglandin E synthase-1, a more downstream and selective point in prostaglandin E2 synthesis than cyclo-

oxygenase itself, and on the nuclear factor kappa B axis that governs the transcription of the cytokines and matrix metalloproteinases driving cartilage loss [6,9]. A single locally delivered agent that reaches leukotriene, prostaglandin and cytokine pathways at once is a different pharmacological proposition from a cyclo-oxygenase-only topical drug, and the target analysis is what makes that difference explicit and quantitative rather than merely asserted.

These findings should be read against the limitations of the methods that produced them, which are real and specific. The descriptor and drug-likeness calculations are among the most reliable in computational chemistry, but the Potts-Guy permeability prediction, as discussed, is a two-parameter model that ignores formulation, is uncertain in the high-lipophilicity range these compounds occupy, and predicts a permeability coefficient rather than an achievable flux; it ranks and screens, it does not measure. The target analysis carries a different and important caveat. Both the boswellic acid target list and the osteoarthritis gene set were compiled from the inflammation literature, and proteins that have been studied intensively in inflammation appear in both, so part of the striking overlap reflects a shared focus of past research as well as genuine biological convergence. The enrichment statistic demonstrates over-representation, not pathway modulation in a joint, and the connectivity of a target reflects how often a congener-target pair has been reported as much as the strength of the interaction. None of the numbers here describes an experiment performed on cells, tissue or an animal, and no conclusion about clinical efficacy follows from them.

What the study does provide is a prioritised and justified route to the bench. It identifies AKBA, or an acetyl-boswellic-acid-enriched extract, as the fraction of choice; it specifies a solubilising lipid nanoemulgel, rather than a simple gel, as the delivery system the drug's solubility-limited flux requires; and it names 5-lipoxygenase, microsomal prostaglandin E synthase-1 and the nuclear factor kappa B axis as the mechanisms a validation study should probe. The concrete experiments that follow are clear: formulate and characterise the nanoemulgel for droplet size, entrapment and rheology, measure ex vivo permeation across skin to test the predicted ranking against real flux, and confirm inhibition of the nominated targets and of downstream mediators such as leukotriene B4 and prostaglandin E2 in a cell or joint-tissue model. The value of the present analysis is that it tells an experimentalist where to spend that effort, and why.

5. Conclusion

A computational profile of the principal boswellic acid congeners shows that their lipophilicity and size, which undermine oral delivery, favour transdermal permeation, and that their molecular targets are enriched more than 400-fold among osteoarthritis-associated genes. Taken together these predictions make a coherent, mechanism-based case for a solubilising nanoemulgel of an AKBA-enriched

boswellic acid fraction as a locally acting, anti-inflammatory transdermal therapy for osteoarthritis, and they define the specific compound, delivery system and molecular targets that laboratory validation should now address. The findings are hypotheses with numbers attached, and their worth is in directing the experimental work that must follow.

Declarations

Consent for publication. Not applicable.

Conflicts of interest. The author declares no competing interests.

Author contributions. The author conceived the study, performed the computational analyses, interpreted the results and wrote the manuscript.

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