

1 **Table S1. The major advantages and potential limitations of small molecules in comparison to larger**
 2 **molecules**

| Advantages | Limitations |
|--|---|
| <p>High potency</p> <p>Small molecules can be developed to have a significant therapeutic impact at low dose when compared to larger molecules</p> | <p>Easy to replicate in market</p> <p>Small molecules simplicity leaves them more open to competition from generic equivalents. On the other hand larger, more complex drugs are harder to replicate and therefore face less competition</p> |
| <p>Cost-effective production</p> <p>Small molecules are effective at smaller amounts of their active pharmaceutical ingredient (API), therefore they are more cost effective in comparison to the large molecule drugs</p> | <p>Low Specificity</p> <p>Basically, the specificity of small molecules is lower than larger molecules such as peptides or other biological agents</p> |
| <p>High quality</p> <p>Today, the technology for developing several small molecules is advanced in pharmaceutical companies to maintain the exceptional reproducibility and the original efficacy</p> | |
| <p>Oral delivery</p> <p>The small molecular weight and size of small molecules means they can be absorbed easily via digestive tracts. Consequently, they can be prescribed in oral form without the requirement of injection</p> | |
| <p>Stability</p> <p>In contrast to several biological agents, most small molecules typically do not need the cold chain assurance required by large molecule drugs which improves their shelf-life and shipping process</p> | |

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Table S2. An overview of small molecules used for IVD regeneration

| Small molecule | Molecular weight | Definition |
|----------------------------|------------------|--|
| Natural origin | g/mol | |
| Cannabidiol | 314.46 | The major nonpsychotropic phytocannabinoid of the marijuana plant (<i>Cannabis sativa</i>). In contrast to major cannabinoids such as Δ^9 -THC, CBD does not cause any psychotomimetic or cognitive effects |
| Epigallocatechin 3-gallate | 458.37 | A biologically active polyphenolic catechin found in green tea (<i>Camellia sinensis</i>) |
| Naringin | 580.54 | A natural flavonoid found in citrus fruits particularly grapefruit where Nar is responsible for the fruit's bitter taste |
| Urolithin A | 228.20 | Urolithins, which are thought to be the intestinal microbial metabolites of both ellagitannins and ellagic acid, include urolithin A, urolithin B, urolithin C and urolithin D. |
| Rhein | 284.22 | Also known as cassic acid, is a substance in the anthraquinone group obtained from rhubarb. Like all such substances, rhein is a cathartic. |
| Estradiol | 272.36 | An estrogen steroid hormone and the major female sex hormone |
| Curcumin | 368.38 | For centuries the root curcuma longa L. (diferuloylmethane) has been used in traditional Chinese and Indian medicine for the treatment of diabetic wounds, hepatic disorders rheumatism and sinusitis |
| o-Vanillin | 152.15 | The metabolites of curcumin with better bioavailability, water solubility and chemical instability which therefore gained importance in research |
| Icariin | 676.66 | The natural flavonoid glucoside which has been used in traditional Chinese Medicine as the herb <i>Epimedium brevicornum</i> in the treatment of a variety of diseases |
| Resveratrol | 228.24 | The potent antioxidant and natural polyphenol which is produced by numerous plants as a phytoalexin, in defense of the plant against irradiation and infectious agents, and is found, as a result in many fruits such as grapes skin and seeds, and therefore wine, as well as peanuts in high amounts |
| Celecoxib | 381.37 | Cyclooxygenase Inhibitors have been successfully in use for the treatment of pain and inflammatory disorders, including the degenerative disc disease, since many decades |
| Kaempferol | 286.23 | A flavonoid agent which has been used as an herb in traditional Asian medicine for centuries for the treatment of abdominal pain, hypertension and headaches, as well as rheumatism. |
| Berberine | 336.36 | The isoquinoline alkaloid which is a plant extract that exerts anti-inflammatory, anti-oxidative and anti-apoptotic properties and is used as an herbal medicine in a variety of diseases |
| Chemical/Synthetic | | |
| Statins | 404.54-558.64 | These drugs were initially developed to treat hyperlipidaemia, they had more pleiotropic effects from cardiovascular to bone regeneration which are mediated by inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase |
| Metformin | 129.16 | Developed in 1922, Met has been the widely used oral medication for type II diabetes worldwide |
| APO866 | 391.51 | Also known as FK866, is an inhibitor of nicotinamide phosphoribosyltransferase |
| Dexmedetomidine | 200.28 | An anxiety reducing, sedative, and pain medication |
| SM04690 | 505.55 | A small-molecule inhibitor of the Wnt pathway |
| Gefitinib | 446.90 | A Food and Drug Administration-approved small molecule which inhibits epidermal growth factor receptor (EGFR) activity by competing with ATP binding to the receptor's kinase pocket |
| Tofacitinib | 312.36 | (Or CP-690,550) an orally administered JAK antagonist that is in development for the treatment of rheumatic arthritis and other immune disorders |
| Luteoloside | 448.37 | (Or Cynaroside) a flavone, a flavonoid-like chemical compound |
| INK-128 | 309.33 | (Or Sapanisertib) a potent and selective mTOR inhibitor |
| NVP-BEZ235 | 469.54 | (Or Dactolisiban) an imidazoquinoline derivative acting as a PI3K inhibitor |
| MK-2206 | 407.47 | An allosteric AKT inhibitor which used for treatment of cancer |

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Table S3. Effective concentrations of small molecules *in vitro* for the regeneration of disc cells

| Small molecule | Effective concentration (<i>in vitro</i>) | Ref. |
|----------------------------|---|-----------|
| Natural origin | | |
| Cannabidiol | 5 μ M | [58] |
| Epigallocatechin 3-gallate | 10 μ M | [50] |
| | 10 μ M | [78] |
| Naringin | 20 μ g/ml | [87] |
| | 60 μ M | [128] |
| | 20 μ g/ml | [129] |
| | 100 μ M | [130] |
| Urolithin A | 20 μ M | [94] |
| Estradiol | 1 μ M | [65] |
| | 1 μ M | [89] |
| | 1 μ M | [131] |
| | 10 μ M | [133] |
| Curcumin | 20 μ M/ml | [145] |
| o-Vanillin | 100 μ M | [104] |
| Icariin | 40 μ M | [138] |
| Resveratrol | 200 μ mol/L | [82] |
| | 100 μ M | [81, 140] |
| Kaempferol | 100 μ M | [52] |
| Berberine | 25 μ M | [53] |
| Chemical/ Synthetic | | |
| Statins | 3 μ M (simvastatin) | [106] |
| | 5 μ M (lovastatin) | [107] |
| Metformin | 10 mM | [59] |
| | 200 μ M | [92] |
| APO866 | 10 nM | [93] |
| Dexmedetomidine | 5 μ M | [74] |
| SM04690 | 11 nM | [109] |
| Tofacitinib | 2.5 mg/mL | [60] |
| Gefitinib | 10 μ M | [20] |
| Luteoloside | 10 μ M | [57] |
| INK-128 | 50 μ M | [102] |
| NVP-BEZ235 | 50 μ M | [102] |
| MK-2206 | 50 μ M | [102] |

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Table S4. Potential clinical application of small molecules in IDD based on *in vivo* studies

| Potential clinical application | Types of application | +/- Supplementation | Ref. |
|---------------------------------------|--|---------------------------|-----------|
| Degenerated disc (grade I-III) | | | |
| Cannabidiol | Local delivery (ID) | - | [127] |
| Naringin | Systemic delivery (IP) | - | [63] |
| Luteoloside | Systemic delivery (IP) | - | [57] |
| Urolithin A | Systemic delivery (PO) | - | [54] |
| Estradiol | Systemic delivery (PO, SC) | - | [121,132] |
| Curcumin | Systemic delivery (IP) | - | [145] |
| Metformin | Systemic delivery (IP) | - | [92] |
| Icariin | Systemic delivery (IP) | - | [146] |
| Resveratrol | Local delivery (ID) | - | [91] |
| Celecoxib (CXB) | Local delivery (ID) | CXB loaded microsphere | [61,141] |
| Berberine | Systemic delivery (IP) | - | [86] |
| Gefitinib | Local delivery (ID) | - | [20] |
| Radicular and discogenic pain | | | |
| Epigallocatechin 3-gallate | Local delivery (injection into underlayer of epineurium) | - | [50] |
| Celecoxib (CXB) | Local delivery (ID) | CXB loaded in hydrogel | [115] |
| SM04690 | Local delivery (ID) | - | [109] |
| Statins | Local delivery (ID) | Statin loaded in hydrogel | [142] |
| Resveratrol | Local delivery (injection into underlayer of epineurium) | - | [117] |

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ID: Intradiscal, IP: Intraperitoneal, SC: Subcutaneous, PO: Peroral