Extracting evidence of supplement-drug interactions from literature

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Abstract

Dietary supplements are used by a large portion of the population, but information on their safety is hard to find. We demonstrate an automated method for extracting evidence of supplement-drug interactions (SDIs) and supplement-supplement interactions (SSIs) from scientific text. To address the lack of labeled data in this domain, we use labels of the closely related task of identifying drug-drug interactions (DDIs) for supervision, and assess the feasibility of transferring the model to identify supplement interactions. We fine-tune the contextualized word representations of BERT-large using labeled data from the PDDI corpus. We then process 22M abstracts from PubMed using this model, and extract evidence for 55946 unique interactions between 1923 supplements and 2727 drugs (precision: 0.77, recall: 0.96), demonstrating that learning the task of DDI classification transfers successfully to the related problem of identifying SDIs and SSIs. As far as we know, this is the first published work on detecting evidence of SDIs/SSIs from literature. We implement a freely-available public interface supp.ai to browse and search evidence sentences extracted by our model.

1 Introduction

More than half of US adults use dietary supplements [16]. Supplements include vitamins, minerals, enzymes, and other herbal and animal products. Although the pharmacological effects of many supplement ingredients remain uncertain due to limited FDA regulation [1], there has been substantial documentation of adverse interactions between supplements and pharmaceutical drugs [24, 11, 13]. Some studies describe the prevalence of supplement-drug interactions (SDIs) in the hospital setting [19, 20, 21] or among specific patient demographics such as patients with cancer [2], cardiac disease [17], HIV/AIDS [14], or Alzheimer’s disease [33]. However, these studies largely rely on manual curation of the literature, and are slow and expensive to produce and update. It is also difficult to aggregate their results, and researchers, clinicians, and consumers can lack appropriate and up-to-date information to make informed decisions about supplement use.

Consumer-facing websites such as the NIH Office of Dietary Supplements [1] or WebMD [2] provide facts about some common supplements, but this information can be incomplete. Results from the latest studies may be lacking due to bottlenecks of manual curation by domain experts. While there exist dedicated clinical resources such as naturalmedicines.com [3] or UpToDate [4] that contain high

[1] https://ods.od.nih.gov/
[2] https://www.webmd.com/vitamins/index
[3] https://naturalmedicines.therapeuticresearch.com/
[4] https://www.uptodate.com/

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quality, curated evidence, these resources may not be broadly accessible due to their subscription format. Drug databases such as DrugBank [40], RxNorm [24], and the National Drug File Reference Terminology (NDFRT) [32] focus on drugs and contain incomplete coverage of dietary supplement terminology [23]. Supplement terms covered by these databases may also lack adequate information, e.g., rarely do they contain information on SDIs reported in the clinical literature.

Clinicians and consumers are limited in their ability to review literature pertaining to SDIs. A resource that provides easily accessible SDI information with experimental evidence supporting these interactions could help both clinicians and consumers in determining appropriate uses of supplements and identifying risks before they lead to adverse events.

Automated approaches have been used to extract drug-drug interactions (DDIs) from literature and other documents [35, 29, 31, 18, 42, 27, 22]. These techniques complement existing methods for identifying DDIs, which are largely based on manual literature review and curation of evidence [12]. We expand upon this prior work to automatically extract evidence for SDIs, as well as supplement-supplement interactions (SSIs), from a large corpus of biomedical and clinical literature (approximately 22M abstracts), and surface the extracted evidence for browsing and search. Due to similarities between DDIs and SDIs/SSIs, we hypothesize that a classifier trained to identify DDI evidence should perform well in identifying SDI and SSI evidence. We therefore take advantage of existing labeled data for categorizing DDIs to train and tune our supplement interactions evidence extractor. Our contributions are:

1. A model for extracting SDI and SSI evidence from literature
2. A set of more than 155k evidence sentences supporting various SDIs and SSIs extracted from 22M abstracts of biomedical and clinical publications
3. A public user interface for browsing and searching the extracted evidence

2 Methods

In this section, we describe our methods for extracting evidence of SDIs/SSIs from biomedical literature. An overview of the procedure is given in Figure 1. We first retrieve articles with PubMed identifiers using the Semantic Scholar API [5] then use scispaCy [25] to identify supplements and drugs in paper abstracts and link them to concepts in the Unified Medical Language System (UMLS) (Section 2.2). We then feed sentences containing mentions of supplement and drug entities (Section 2.1) into our BERT-DDI model, a neural network classifier based on BERT [8] and trained on labeled DDI data from Ayvaz et al [5] (Section 2.3). Sentences classified as positive instances by the BERT-DDI model are then collated and surfaced on a web-based interface (Section 4), freely-available for researchers, clinicians, and consumers, located at https://supp.ai/.

2.1 Supplement and drug identifiers

To identify supplements and drugs, we generate lists of UMLS Concept Unique Identifiers (CUIs) using a semi-automated process. We first identify high level classes and rules over UMLS concepts that identify supplements or drugs with high recall. For supplements, we identify NCI thesaurus

https://api.semanticscholar.org/
(NCIT) concepts such as “Dietary Supplement” (NCIT: C1505, CUI: C0242295), “Vascular Plant” (NCIT: C14336, CUI: C0682475), and “Antioxidant” (NCIT: C275, CUI: C0003402) as parent entities for likely supplements. Using UMLS relationships, we recursively extract child entities of these parent classes, deriving an initial list of supplements. To add additional entities to this list, we extract supplements from the TRC Natural Medicines database and perform a fuzzy name match to entities in UMLS, and add matching CUIs to our list of supplements. The list is manually reviewed to remove non-supplement entities, things more commonly known as foods, weeds, herbicides, or other entities for which we could not identify any marketed supplements or medicinal uses. Following curation, we retain 2139 unique supplement entities.

Similarly, we generate a corresponding list of drug CUIs. Parent entities used to initialize the drug CUI list are “Pharmacologic Substance” (NCIT: C1909, CUI: C1254351) and any UMLS entity with a DrugBank identifier. Fuzzy name matching between drugs on drugs.com and UMLS entities is used to identify drugs and experimental chemicals missed through UMLS search alone. Due to the significantly larger number of drugs, manual curation is impractical at this time; we allow the detection of SDIs to perform additional filtering on the drug list (operating on the supposition that non-drug entities are very unlikely to participate in a SDI interaction with any of our supplements). This process generates a list of 15252 unique drug CUIs.

Any entity that is both a supplement and a drug under the above rules is categorized exclusively as a supplement. This ensures maximal coverage of interactions for any entity that can be used as a supplement. As discussed in more detail later, the boundary between pharmaceutical drugs and supplements can be ambiguous, and although these mutually exclusive classifications may not be precise, they suffice for our purposes.

We additionally introduce a semi-automatically curated set of clusters, indicating UMLS entities that should be merged for this particular task. Similar chemical species are merged, e.g. the entities corresponding to UMLS C0006675, C0006726, C0596235, and C3540037 all describe variants of Calcium and are merged under the supplement entity C3540037 (“Calcium Supplement”).

### 2.2 Extraction of candidate evidence

Around 22M articles are downloaded using the Semantic Scholar API. To limit the articles we retrieve to the biomedical domain, we only fetch articles that have been indexed by Medline.

The scispacy-small model is used to process all downloaded paper abstracts. The scispacy model performs named entity recognition (NER) and sentence tokenization. We also use the entity linking feature in scispacy to link entity mentions to UMLS CUIs. We elect to use scispacy in lieu of other UMLS entity linkers such as MetaMap primarily due to performance requirements.

To reduce the number of entities, we use UMLS semantic type to filter linked entities by type, keeping only entities of types more likely to be drugs or supplements. These types are:

- T002: Plants
- T109: Organic chemical
- T116: Amino acid, peptide, or protein
- T120: Chemical viewed functionally
- T121: Pharmacologic substance
- T125: Hormone
- T127: Vitamin
- T129: Immunologic factor
- T195: Antibiotic
- T196: Element, ion, or isotopes
- T197: Inorganic chemical
- T200: Clinical drug

These semantic types were selected to maximize coverage of supplement and drug entities. Reserving all entities of these types allows us to iterate quickly upon the supplement and drug CUI lists.

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6 https://naturalmedicines.therapeuticresearch.com/
7 https://drugs.com/
8 Of these articles, 8.4M contain full text. Evidence from full text is not surfaced in the current prototype, and we leave the incorporation of this additional evidence to future work.
developed in Section 2.1. Even if new entities are added to the known identifier lists or moved between them, we can still capitalize on previous NER and linking results (as the semantic type filters have higher recall than the rules used to generate the supplement and drug identifier lists).

As an example, entities in the following sentence from Vaes and Hendeles [36] are linked to their corresponding UMLS CUIs:

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Hemorrhage and tendencies were noted in four cases with ginkgo use and in three cases with garlic; in none of these cases were patients receiving warfarin.
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The top linking result for each span is shown. Entities in blue match our filtered semantic types. We retain spans where any of the top three linking results correspond to one of these semantic types, and select the top scoring CUI for that span. For example, “ginkgo” is linked to C0330205 (T002), C3531686 (T109, T121), and C0772125 (T109, T121), and we select C0330205 the top scoring CUI. To improve precision, we eliminate any mention spans that link with high confidence (scispaCy linking score > 0.95) to a UMLS concept that does not belong to one of these semantic types. This reduces the number of incorrectly linked spans containing very general word tokens which happen to overlap with names or aliases of supplement or drug entities.

From these results, we retain all sentences containing at least two entity mentions. For these sentences, we take every combination of two entity spans where one corresponds to a supplement entity, and another corresponds to a drug or supplement entity on our lists. Following all filtering steps, around 29.5M sentences with unique span pairs remain. Each of these sentences is a candidate evidence of SDI or SSI, which is then classified using the BERT-DDI model described below.

### 2.3 BERT-DDI model

Here, we describe the neural model we developed for predicting whether a given sentence marked with a pair of supplement/drug entities provides evidence of an interaction between the two entities.

**Input layer:** The input layer consists of the sequence of WordPiece tokens [41] in a sentence. We replace the mention spans in question with the special tokens [Arg1] and [Arg2]. This helps generalization by preventing the model from memorizing which entity pairs were presented with a positive interaction in the training set. For example:

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[CLS] Combination [Arg1] may also decrease the plasma concentration of [Arg2]. [SEP]
```

where [Arg1] replaces the span “hormonal contraceptives” and [Arg2] replaces the span “acetaminophen.” We add the special tokens [CLS] and [SEP] at the beginning and end of each sentence in order to leverage their representations learned in pre-training. At prediction time, candidate sentences are masked similarly and fed to the trained model.

**Model architecture:** As the name implies, BERT-DDI uses the pre-trained BERT model (Bidirectional Encoder Representations from Transformers) [8] to encode input sequences. The input is encoded using $L$ layers of transformer blocks, each of which consists of bidirectional multi-headed self-attention (with $A$ self-attention heads and hidden size $H$) followed by a feed-forward layer with an output size of $4H$. In particular, we use the BERT-large model with $L = 24$, $H = 1024$, $A = 16$, and a total of 340M parameters. More details of the transformer architecture can be found in [37]. The BERT-DDI adds a dropout layer followed by one feedforward (output) layer, $\mathbb{R}^{2 \times H}$ with a softmax non-linearity, which takes the representation of the [CLS] token at the top transformer layer as input and outputs probabilities for labels $\{0, 1\}$.

**Model training:** Due to the large number of parameters in the encoder (340M), [8] crucially relies on pre-training the encoder by learning to predict masked tokens on a large amount of unlabeled data. We use the pre-trained weights distributed by the authors, and further fine-tune the model parameters
(as well as parameters of the output layer) using labeled datasets for drug-drug interactions (see dataset details in Section 3).

3 Results

Existing datasets of drug-drug interactions: A primary objective of this work is to assess the viability of transferring DDI models for identifying supplement interactions. We train the BERT-DDI model using labeled DDI data derived from the Merged-PDDI combined DDI dataset [5]. In particular, we use training data from the DDI-2013 and NLM datasets, as these two datasets are relatively large (see Table 1 for details) and contain evidence sentences with annotated spans corresponding to drug entities. We collapse the labels which correspond to different types of interaction (e.g., mechanism, advise, effect, etc.) into binary labels of 0 and 1, where 0 means no interaction, and 1 means an interaction of some type exists between the two annotated spans. Collapsing the positive labels is necessary for training one model on both datasets, since the two datasets are inconsistent in their definition of interaction types. We preserve the train/development/test splits used in [5], and use the development set to iterate on model design and tuning.

| Dataset     | Train | Dev. | Test  | Label=1 |
|-------------|-------|------|-------|---------|
| DDI-2013    | 9442  | 1077 | 2026  | 25.0%   |
| NLM corpus  | 16289 | 1947 | 2766  | 24.6%   |

Table 1: DDI training data from Merged-PDDI dataset.

A new dataset of textual evidence for supplement interactions: A key contribution of this work is the collection of textual evidence for supplement interactions, automatically extracted from scientific documents as detailed in the previous section. We retrieve 22M medical articles using the Semantic Scholar API. Of these, around 4.5M article abstracts are identified as relevant in the second step (Figure 1). After all filtering steps, 29.5M sentences are fed to the BERT-DDI model in the third step (Figure 1), each automatically labeled with a pair of entity mentions. Around 1.1M (3.6%) of these sentences are classified as positive for an interaction by our model. Finally, to increase the utility of the extracted evidence, we use the lists of supplement and drug CUIs derived from UMLS to remove irrelevant sentences, and group related evidence based on the clusters described in Section 2.1. Due to licensing constraints with publishers, we cap the sentence length at 50 words and remove extra words in longer sentences.

These evidence sentences mention 1923 unique supplements and 2727 unique drugs. Evidence for these SDIs and SSIs are sourced from 163708 unique papers. Each evidence sentence in this dataset is annotated with two spans describing the supplement and drug entities, as well as the linked UMLS CUIs. Source paper metadata such as title and author are provided for each sentence. Our hope is that this dataset will help enable and facilitate further studies on supplement interactions. \(^9\)

Quality of textual evidence of supplement interactions: To evaluate the quality of extracted evidence on a test set, we sampled 200 sentences and manually annotated them for the presence or absence of a supplement interaction. To obtain a balanced dataset despite the rare presence of a positive interaction, we sampled half the instances from the set of sentences labeled as positive by the BERT-DDI model, and the other half from those labeled as negative by the model. After manual annotation, 40% of the sampled instances were labeled as positive. The annotations were done by two of the authors without seeing model predictions, with an inter-annotator agreement of 94%. This test set was only used for final evaluation, and never used for model development or tuning. Performance of the BERT-DDI model on this test set is reported in the last row in Table 2 showing an accuracy of 87%, precision of 77%, F1 score of 86%, and a notably high recall of 96%.

To further analyze model performance, it is instructive to also consider how it performs on DDI evaluation sets. Although it is natural for a model trained on DDI labels to perform better on DDI test sets, our results suggest that the “in-domain” results are not always better. While the accuracy and

\(^9\) We note that the same sentence may appear multiple times with different entity pairs.

\(^{10}\) https://github.com/lucylw/supp-ai-extracted-sdi-data/
| Evaluation set       | Accuracy | Precision | Recall | F1  |
|---------------------|----------|-----------|--------|-----|
| Drugs (DDI-2013)    | 0.93     | 0.88      | 0.85   | 0.87|
| Drugs (NLM)         | 0.92     | 0.83      | 0.86   | 0.84|
| SDI/SSI             | 0.87     | 0.77      | 0.96   | 0.86|

Table 2: The BERT-DDI model (trained on drug-drug interaction labels) is evaluated on two DDI evaluation sets (first two rows) and our supplement interaction evaluation set (last row).

precision of the model are significantly higher on the DDI datasets, the recall is lower and the F1 score is comparable. In fact, the improved accuracy on DDI test sets can be attributed to the smaller percentage of positive instances in these test sets (roughly 25% in both DDI test sets, compared to 40% in the supplements test set).

Another important difference which can explain the lower performance of BERT-DDI on identifying supplement interactions is the presence of incorrectly labeled entity spans in the supplements test set. To gain a better understanding of how significant this source of errors may be, we also evaluate the performance of the scispaCy entity linker over the PDDI datasets. Processing each sentence from the two dataset through the scispaCy NER and linking pipeline, we determine the number of drug entities successfully linked to a UMLS entity. The results are shown in Table 3. Only 80% of drug entities from DDI-2013 and 76% from NLM are recognized and successfully linked to UMLS CUIs. These numbers provide an estimate of the global ceiling on recall for our model.

| Corpus     | Precision | Recall | F1  |
|------------|-----------|--------|-----|
| DDI-2013   | 0.50      | 0.80   | 0.61|
| NLM        | 0.51      | 0.76   | 0.61|

Table 3: Evaluation results of scispaCy entity linking for drug entities on the Merged-PDDI corpus.

**Examples of extracted evidence:** A qualitative analysis of the extracted evidence clearly demonstrates the practical benefits of using an automated method for extracting supplement interactions to augment or assist manual curation done by experts. We manually assess some interactions identified using our methods, cross-checking against a tool provided by the NIH Office of Dietary Supplements, and found several of them to be missing. For example, a possible interaction between bee pollen and warfarin is reported in [13]:

```
Consumption of [bee pollen] led to increased INR values in a patient taking [warfarin].
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and another between genistein and insulin is reported in [26]:

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[Genistein] (100 microM) time-dependently increased [insulin] mRNA levels in INS-1 cells.
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Neither interaction was listed on the NIH tool at the time of this writing.

## 4 Supplement interaction browser

The supplement interactions extracted using this work have immediate implications on public health, which can only be realized by making the data easily accessible to any interested researcher, clinician or consumer. We note that many medical providers in developing countries do not have subscriptions

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11 Peng et al [28] report SOTA performance on the DDI-2013 dataset treating the task as multi-class classification with four classes, achieving 0.79 F1 using a tuned BERT-large model. Due to our formulation of DDI detection as a binary classification problem, our performance on DDI-2013 is not directly comparable to [28].

12 [https://ods.od.nih.gov/factsheets/list-all/](https://ods.od.nih.gov/factsheets/list-all/)
to databases such as TRC\(^{13}\) and UpToDate\(^{14}\) and may lack an easy way to identify possible supplement interactions before prescribing drugs to their patients. We also note that some of the interactions we found were not listed in such interaction databases, suggesting that even clinicians who have a subscription to them may benefit from gaining access to the interactions identified using our methods. To fill this gap, we developed a public web-interface \(https://supp.ai/\) for querying and browsing the evidence extracted by our model. The SDI/SSI browser features the ability to:

- Search for supplements or drugs (featuring auto-complete and fuzzy matching),
- List all supplements or drugs that potentially interact with a given queried entity,
- Display evidence sentences with supplement and drug entities highlighted,
- Provide links to papers from which the evidence was extracted, and
- Sort evidence sentences from papers by paper features.

We perform additional extraction of paper metadata as a way to judge evidence quality. From the Semantic Scholar API, we retrieve the paper title, authors, publication venue, and year of publication. We also use Medical Subject Headings (MeSH) tags associated with each paper to determine whether its results are derived from clinical trials, patient studies, case reports, or animal studies. Additionally, we attempt to retrieve the retraction status of each paper. Evidence sentences are then ordered and presented based on associated paper metadata, prioritizing non-retracted studies, clinical trials, human studies, and recency (year of publication).

We also extract tradenames for common drugs. Using the RxNorm relationship has_tradename via UMLS, we derive tradenames associated with ingredients on our list of drugs, e.g. the tradenames Prozac and Sarafem are associated with the ingredient fluoxetine. Drug tradenames with one or few active ingredients are associated with the drug ingredient and indexed for search in our browser. Users can query a tradename rather than an active ingredient and be directed to the same results.

We designed the web application to be a rapid way for users to access and search the extracted SDI and SSI evidence. We plan to periodically update the search interface with the latest information extracted from new papers as they are incorporated into the Semantic Scholar corpus. Our goal for this user interface is to provide a high quality, broadly-sourced, up-to-date, and easily accessible platform for searching through SDI and SSI evidence, while providing sufficient information for users to judge the quality of each piece of evidence.

Figure 2 shows an example of what a user may see when they search for the ginkgo supplement. Initial search results show 140 possible interactions to entities such as Warfarin and Nitric Oxide. When the user selects a specific result, the evidence sentences supporting that interaction are displayed along with links to each source paper.

**Figure 2**: Top results for interactions with Ginkgo (left), and top evidence sentences for the SDI between Ginkgo and Warfarin (right). Source paper metadata are given below each evidence sentence.

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13. \(https://naturalmedicines.therapeuticresearch.com/\)
14. \(https://www.uptodate.com/\)
5 Discussion

Information describing the safety and efficacy of dietary supplements can be difficult to find. The inability to locate appropriate evidence of SDIs can challenge clinicians’ ability to advise patients and cause risks for consumers of dietary and herbal supplements. It is our hope that extracting evidence for SDIs and SSIs from a large corpus of scientific literature and making the evidence available through a easily accessible search interface can offset some of these risks. We envision many uses for this tool, and provide some of them below as motivating examples for future work:

1. Clinicians can assess SDI/SSI risk for their patients by integrating the identified interactions in an alert system such as [3].
2. Researchers can bootstrap a literature review on the interactions associated with a particular supplement.
3. Consumers can investigate the safety of a supplement relative to their existing medications.
4. Ontologists can add novel supplement interactions to databases such as DrugBank or NDFRT.
5. Hospitals can curate this evidence and incorporate high confidence relationships into clinical decision support systems that not only warn against potential DDIs but SDIs/SSIs as well.

In related work, [15] develop a model for identifying adverse effects related to dietary supplements as reported by consumers on Twitter, and discover 191 adverse effects pertaining to 4 dietary supplements. Notably, 48 of the 191 effects were not found in datasets curated by experts such as Natural Medicines Comprehensive Database (NMCD) and drug.com. [10] and [9] analyze unstructured clinical notes to predict whether the patient started, continued or discontinued taking dietary supplements, which can be useful as a building block for identifying adverse effects in clinical notes (as attempted by the same authors in [11] although this study focused on interactions with only one drug: warfarin). [39] proposes using topic models to analyze the adverse effects of dietary supplements as mentioned in the Dietary Supplement Label Data-base (DSLD), and finds that Latent Dirichlet Allocation models [6] can be used to group dietary supplements with similar adverse effects based on their labels. The lack of a standardized terminology to describe dietary supplements is discussed in [23] and [38], with estimates of the UMLS coverage between 14% and 54%, further demonstrating the lack of data resources on dietary supplements.

In this work, we make a distinction between supplements and drugs. In practice, the difference between the two classes of entities is far less clear. Both supplements and drugs are pharmacologic entities, with the distinction more attributable to marketing and social pressures rather than functional differences. However, due to this somewhat arbitrary distinction, supplement entities are less well represented in databases of pharmaceutical entities, and less information is publicly available on their interactions. Our work is an attempt to close this gap.

This work demonstrates how natural language processing techniques can be extraordinarily useful for extracting information and relationships specific to an application domain in healthcare. Clever re-purposing of existing labeled data (that would be expensive to generate in a new domain) can be yet another way to derive maximum utility of curation efforts for solving related problems. Continuing, we aim to leverage similar techniques for identifying evidence of indications, contraindications, and side effects of dietary supplements from the biomedical and clinical literature.

Conclusion

Insufficient regulation in the supplement space introduces dangers for the many users of these supplements. Claims of interactions are difficult to validate without links to source evidence. We train a model to detect SDI/SSI evidence from the scientific literature. Our model successfully leverages labeled training data in a related domain to detect interactions involving supplements at high accuracy. We make the extracted set of SDI/SSI evidence available for download and search-able through a public web interface. This dataset and web interface can be leveraged by researchers, clinicians, and patients to increase understanding about supplement-related interactions. We hope to encourage additional research to improve the safety and benefits of dietary supplements for the healthcare consumer.
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