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An updated overview and classification of bioinformatics tools for MicroRNA analysis, which one to choose?

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ABSTRACT

The term 'MicroRNA' (miRNA) refers to a class of small endogenous non-coding RNAs (ncRNAs) regenerated from hairpin transcripts. Recent studies reveal miRNAs' regulatory involvement in essential biological processes through translational repression or mRNA degradation. Recently, there is a growing body of literature focusing on the importance of miRNAs and their functions. In this respect, several databases have been developed to manage the dispersed data produced. Therefore, it is necessary to know the parameters and characteristics of each database to benefit their data. Besides, selecting the correct database is of great importance to scientists who do not have enough experience in this field. A comprehensive classification along with an explanation of the information contained in each database leads to facilitating access to these resources. In this regard, we have classified relevant databases into several categories, including miRNA sequencing and annotation, validated/predicted miRNA targets, disease-related miRNA, SNP in miRNA sequence or target site, miRNA-related pathways, or gene ontology, and mRNA-miRNA interactions. Hence, this review introduces available miRNA databases and presents a convenient overview to inform researchers of different backgrounds to find suitable miRNA-related bioinformatics web tools and relevant information rapidly.

1. Introduction

Micro RNAs (miRNAs) are defined as a class of non-coding single-stranded RNAs about ~22 nucleotides in length. Computational predictions have evaluated that over 60% of transcripts in the human genome may be regulated by miRNAs [1]. MiRNAs can bind to specific target mRNAs by selective base–pairing, often in the 3′-untranslated region (3′UTR) and more rarely 5′-untranslated region (5′UTR) [2]. These molecules are involved in regulating gene expression at the post-transcriptional level through translational repression or degradation mechanisms [3]. A miRNA can regulate multiple mRNAs, and conversely, multiple miRNAs can modulate mutual mRNA targets [4,5]. The gene coding miRNAs are usually found in both intergenic and intragenic areas, as well as in sense or antisense strands within introns of genes, and are mostly transcribed by RNA polymerase II [3,6]. The RNA polymerase II (Pol II) produces primary (pri)-miRNA, which is cleaved into smaller stem-looped structures, known as a precursor (pre)–miRNA, by Drosha as an RNase III endonuclease, and its cofactor, DGCR8 [7]. Then, the pre-miRNA is transported from the nucleus to the cytoplasm by Exportin-5 protein and RAN GTPase [8]. Finally, in the cytoplasm, an RNA III-like enzyme called DICER produces mature miRNA from pre-miRNA. According to the complementary degree in connecting with targets, mature miRNAs perform their regulatory function by two posttranscriptional mechanisms: cleavage or repression of the translation of their targeted mRNAs (Fig. 1) [9]. The mechanism of translational repression by miRNAs is not entirely understood, but it is supposed that miRNAs inhibit translation in elongation or termination phases, or destroy the polypeptide released from the ribosome [10,11].

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miRNAs might temporarily bind and modify mRNAs, or stably bind to their targets and employ factors mediating translational repression [12]. Also, transcription or splicing of transcripts in the nucleus can be regulated by miRNAs [13,14]. Based on the role of miRNAs in biological processes, disruption in their biogenesis or regulation can lead to diseases [15]. MiRNAs have been investigated in different diseases, including vascular diseases [16], neurological disorders [17,18], and cancers [19–21]. Therefore, identification of miRNAs and their targets can be considered as new diagnostic and therapeutic approaches [13, 22–24]. According to technological developments, such as bioinformatics tools/software and sequencing methods, a large number of miRNAs have been identified in various organisms. Based on the latest version of the miRBase (V22), there are more than 48800 different mature miRNA sequences [25,26]. In the past decades, studies on miRNAs and their related fields have increased at a tremendous pace generating a large amount of scattered data. Several bioinformatics tools have been developed to manage these data. These databases can be categorized based on the information they provide for users. However, each database applies different algorithms and parameters that may be difficult to understand for users with little/no experience in this respect. In the present article, we aim to overview the significant classes of miRNA databases, explain essential features of each, and discuss how to select appropriately among them. Overall, we offer some important considerations on using the mentioned tools for miRNA analysis.

2. Overview of bioinformatics tools used in miRNA research

Nowadays, to manage the vast miRNA-related data, several bioinformatics tools have been expanded. Based on the platform used, these tools can mainly fall into three categories of packages, downloaded software, and web-based services. Web-based services are the most convenient platform since they provide the opportunity for simple data entry with possibilities for modification and specific output information. In addition, they are the best choices for users with insufficient bioinformatics knowledge [27]. Unfortunately, the web-based tools have disadvantages including inadequate results and false positive/negative existence in outputs and scant overlap in database algorithms [28]. Due to the lack of enough sensitivity, recent bioinformatics algorithms cannot identify all of the confirmed miRNA: target interactions (MTI) [29].

Furthermore, some tools are not currently operational or are outdated because of the absence of an option to enter updated data [30]. Therefore, it is recommended to use various suitable and updated algorithms synchronously to overcome these shortcomings (studies required ranking are an exception) [31]. Since different miRNA-related online tools present diverse information, the principal objective of this review is to classify them based on their primary usage (Fig. 2). In summary, databases included in these categories are presented in two tables: databases for finding target genes are summarized in Table 1, and those designed based on other aspects of microRNAs required in research areas are listed in Table 2.

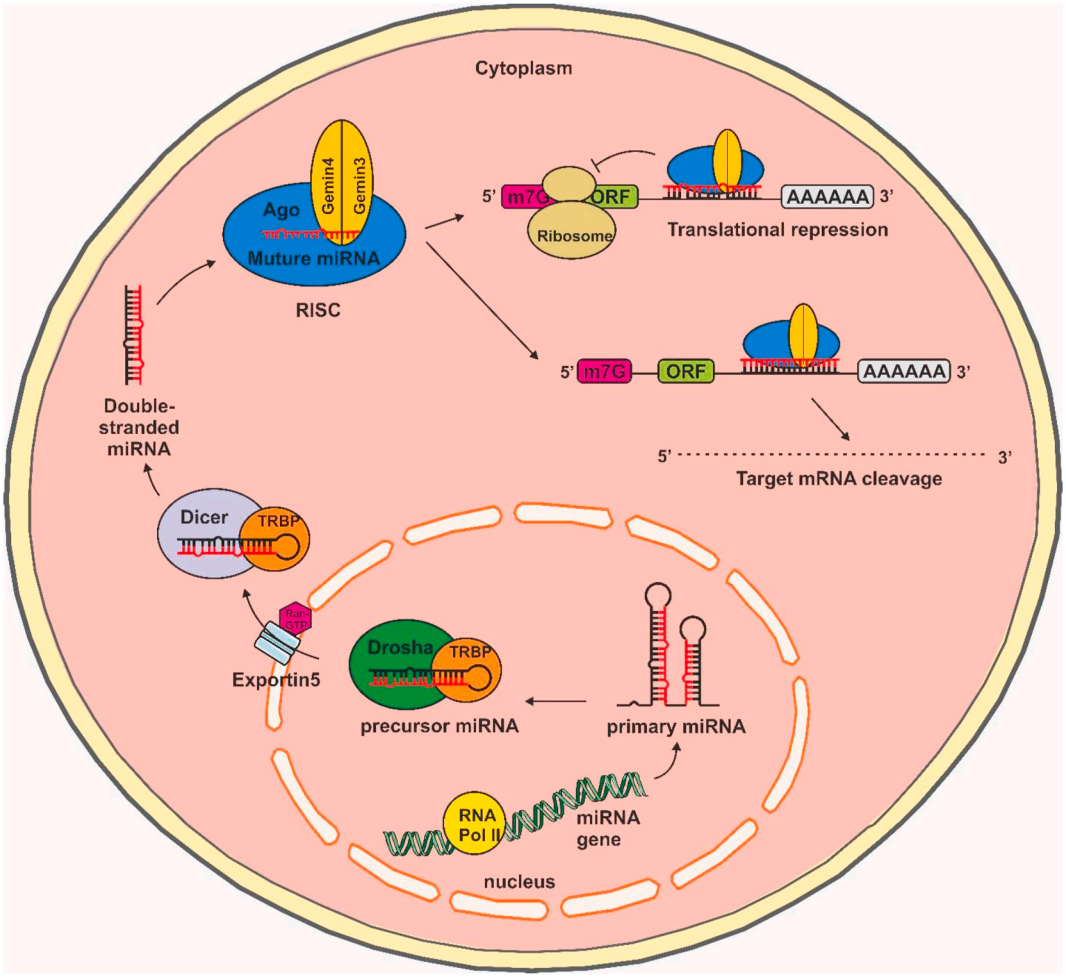

Fig. 1. A schematic overview of the biogenesis and function of miRNAs in animals. miRNA genes transcribed to pre-miRNA, and subsequently proceeded to mature miRNAs. Mature miRNA can bind to mRNAs, targets of miRNA, and act through two procedures: (1) cleavage of target mRNA, and (2) translational inhibition.

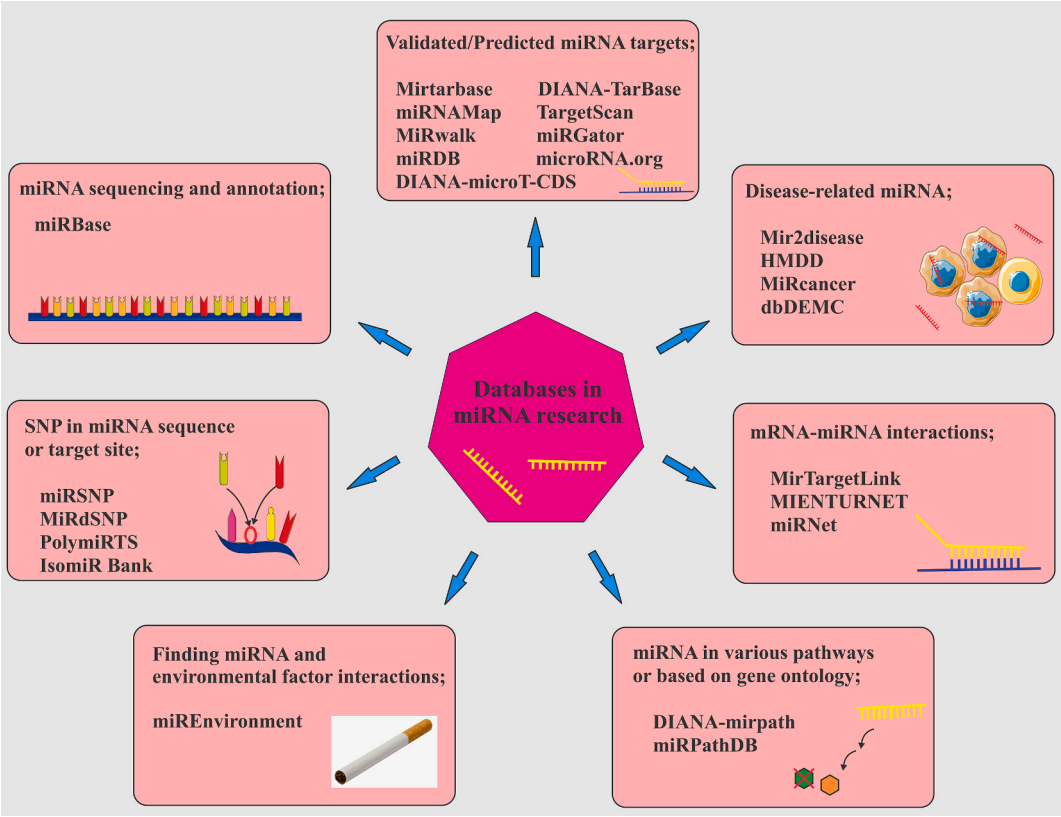

Fig. 2. Overview on bioinformatic tools are used in miRNA. There are various kinds of tools helping to find more about miRNAs sequencing, mRNA-miRNA interactions, pathways they are involved in, miRSNPs, disease-related miRNAs, and miRNAs target.

3. Database for finding miRNA sequencing and annotation

3.1. MiRBase

miRNA identification is complicated and requires high-throughput technologies [32]. Nevertheless, recently thousands of miRNAs have been discovered in eukaryotes and viruses [33–35]. The miRbase (V22) (http://www.mirbase.org/), 48860 mature miRNAs and 38589 hairpin precursors from 271 organisms are collected in this database. miRbase can be considered as the main primary online repository providing a resource for miRNA sequences and annotations [26,36]. Also, the miRbase presents a wide range of published miRNAs information, including stem-loop structure (termed mir), deep sequencing read number mature miRNA (termed miR) of both 5p and 3p, position, literature references, linking out to other resources such as miRNA target prediction databases, methods of identification, and familial relationships. On the other hand, this database represents a comprehensive reference for achieving desired miRNA feature by different aspects such as keyword, accession number, name, genomic location, clusters, tissue expression, and most importantly, based on the sequence of hairpin precursor or mature miRNAs. The Browse page displays a list of diverse species with reported miRNAs. The information of the species are summarized in the table including name, accession number, and genomic details in the selected organism [26,37–43].

4. Databases for finding validated/predicted miRNA targets

4.1. Finding predicted miRNA targets

Target prediction analysis is performed for two primary reasons: First, to provide support for future experimental validation of the predicted interactions between miRNAs and their targets *in silico*; second, to find the most suitable candidates for gene ontology (GO) enrichment analysis and to determine the biological processes where these miRNAs are involved [31]. With improved algorithms of target prediction and detailed miRNAs knowledge, different computational online tools have been developed to predict proper targets for miRNAs [44]. According to predictive strategies, the most common factors affecting a miRNA's ability for binding to its target can be classified into four groups of seed match, thermodynamic stability or the Gibbs free energy of the MTIs, evolutionary conservation, and site accessibility, as well as less common features such as local AU content [30]. The seed region of miRNAs (nucleotides 2–7 in the 5′ region of miRNAs) is essentially considered for mRNA targeting [44,45]. Based on the criteria and stringency, each target prediction tool considerably produced different results containing many false/negative predictions as well as the best set of candidate targets [31]. For most available algorithms, Watson–Crick base pairing with the target region is required, which can decline the false/positive prediction incidence [44]. Therefore, finding effective procedures is essential to decrease the number of false-positive predicted targets [28]. Generally, combining results from multiple prediction and validation tools is often recommended to minimize false positive and/or negative outputs [31]. Also, since every tool uses specific updates of miRBase, regular updating is another problem because of changes in the definition and annotation of miRNAs among various versions of miRbase. Therefore, various tools are presented for querying, converting, and retrieving the information of miRNAs among miRBase different versions [46].

In recent years, several online computational tools for miRNA-target prediction have been developed. Available algorithms have been broadly reviewed in many articles considering their bioinformatics, as well as mathematical and statistical characteristics [47–49]. Therefore, in the following section, we briefly discuss some of those databases used most commonly in medicine and life science research.

Table 1
Databases for finding targets.

Name	Species	Collected Data	Last Update	miRbase version	URL	Ref.
miRTarBase 8.0	32 Species, including human	miRNA basic information Target experimental Predicted target Diseases/pathways Literature mining Target expression miRNA expression	2020	miRBasev.22	http://miRTarBase.cuhk.edu.cn/.	[25,53]
DIANA-TarBase:	18 Species, including human	miRNA basic information Target experimental Predicted target Diseases/pathways Target expression	2017	miRBasev.21	http://carolina.imis.athena-innovation.gr/diana_tools/web/index.php?r = tarbasev8%2Findex	[54,56]
TargetScan	10 Species, including human	Predicted target	2018	miRBasev.21	www.targetscan.org	[27,45,59,119]
MiRwalk	5 species, including human	miRNA basic information Target experimental Predicted target Diseases/Pathways Literature mining miRNA-ncRNA interaction Target expression miRNA expression	2018	miRBasev.22	http://zmf.umm.uni-heidelberg.de/apps/zmf/mirwalk2/	[60]
miRNAMap	12 Species, including human	miRNA basic information Target experimental Predicted target Target expression miRNA expression	2008	miRBasev.9.2	http://mirnamap.mbc.nctu.edu.tw/html/tutorial.html	[57]
miRGator	human	miRNA basic information Target experimental Predicted target Diseases/Pathways Target expression miRNA expression	2013	MiRBase v. 18	http://mirgator.kobic.re.kr/index.html	[62]
miRDB	5 Species, including human	miRNA basic information Predicted target Literature mining	2020	miRBase V22	http://mirdb.org/index.html	[63–65]
microRNA.org	5 Species, including human	miRNA basic information Predicted target miRNA expression	2010	miRBase V15	http://www.microrna.org	[2,68]
DIANA-microT-CDS	4 Species, including human	miRNA basic information Predicted target	2013	miRBase V18	http://www.microrna.gr/webServer	[69–71]

4.2. Finding validated miRNA targets

Whichever efficient prediction tool has been utilized to predict miRNA:mRNA interactions, results should always be confirmed experimentally. Techniques commonly employed for experimental validation include qRT-PCR, Western blots, Luciferase reporter assays, and Microarrays, and some high-throughput methods including RNA-Seq, CLIP-seq, and CLASH [50,51]. Some databases containing information on experimentally validated miRNA targets are developed to investigate relevant literature and data collections. Major databases used in finding validated/predicted targets are described below and listed in Table 1. However, some target prediction tools were omitted for different reasons some of which are mentioned in Table 3.

4.3. Mirtarbase

miRTarBase is an important source for the most recent and comprehensive data of validated MTIs regularly updated by manually surveying research. miRTarBase includes the largest collection of validated MITs compared to the other databases and is updated more often than other mentioned databases. The first version of miRTarBase was launched in 2011 [52]. Since 2011, miRTarBase has been applied in various research fields: improving the target prediction accuracy rate, incorporating miRNA databases and other web-based tools, and detecting regulatory networks of miRNA-mRNA in diseases like cancer. Therefore, this database presents not only targets but also the regulators of miRNAs, and allows the users to investigate the miRNAs' down- and upstream regulations. In version 8.0, a text-mining system was applied to increase the recognition of articles concerning MTIs by adopting a scoring system. To provide data on the miRNAs' regulatory network and their expression in blood, and to enhance the academic value, miRTarBase combined biological databases including miRBase, NCBI Entrez gene, and NCBI Refseq (Gene and miRNA related databases), HMDD (miRNA: disease association Database), CMEP, Gene Expression Omnibus (GEO), and The Cancer Genome Atlas (miRNAs expression data). MTIs provided in Mirtarbase have been validated with different experimental methods, including western blotting analysis, luciferase reporter assay, and other high-throughput methods [25,53].

Table 2
Databases related to different aspects of miRNAs.

Databases category	Tool	Species	Data Collection	last update	URL	Ref
Disease related	Mir2disease	Human	miRNA basic information Target experimental Predicted target Diseases/Pathways Literature mining miRNA expression	2008	http://www.mir2disease.org	[85]
	HMDD	Human	Target experimental Diseases/Pathways Literature mining	2019	http://www.cuilab.cn/hmdd	[86,88,120]
	miRCancer	Human	Diseases/Pathways Literature mining miRNA expression	2020	http://mircancer.ecu.edu	[90,91]
	DIANA-mirpath	Seven Species, including human	Target experimental Predicted target Diseases/Pathways	2015	http://snf-515788.vm.okeanos.grnet.gr/	[105,106]
	dbDEMC	Human	High-throughput expression data analysis	2017	https://www.biosino.org/dbDEMC/index	[92,93]
Pathways related	miRPathDB	Human, mouse	Target experimental Predicted target Diseases/Pathways	2019	https://mpd.bioinf.uni-sb.de/	[107–109]
Environmental factor related	miREnvironment		miRNA basic information Environmental factor information Diseases/Pathways	2012	http://www.cuilab.cn/miren	[100,101]
SNP related	MirSNP	Human	miRNA basic information Predicted target miRNA-SNP related information	2012	http://bioinfo.bjmu.edu.cn/mirsnp/search/	[94]
	MiRdSNP	Human	Target experimental Predicted target Diseases/Pathways miRNA-SNP related information	2012	http://mirdsnp.ccr.buffalo.edu/	[97]
	PolymiRTS	Human, mouse	miRNA basic information Target experimental Predicted target Diseases/Pathways miRNA-SNP related information	2013	http://compbio.uthsc.edu/miRSNP/	[98,121]
	Mirsnpscore	Human	miRNA basic information Predicted target miRNA-SNP related information	2011	http://www.bigr.medisin.ntnu.no/mirsnpscore/	[122]
	MicroSNiPer	Human, mouse	miRNA basic information Predicted target miRNA-SNP related information	2012	http://vm24141.virt.gwdg.de/services/microsniper/	[123]
	miR-isomiRExp	Human	miRNA basic information miRNA-SNP related information Diseases/Pathways IsomiRs information	2016	http://server.malab.cn/miRisomiRExp/index.jsp	[124]
	IsomiR Bank	Eight species, including human	miRNA basic information IsomiRs information Predicted target Experimental data miRNA-SNP related information	2016	https://mcg.ustc.edu.cn/bsc/isomir/	[99]
	miRNASNP	Nine Species including human	miRNA basic information,	2015	http://bioinfo.life.hust.edu.cn/miRNASNP2/	[125,126]

Table 3
Omitted databases.

Tools	Reason for deletion	ref
Pictar	Based on data that is over 10 years out of date	[127,128]
NBmiRTar	Data is over 10 years out of date and Tools are not operational anymore	[129]
miTarget	Data is over 10 years out of date and Tools are not operational anymore	[130]

4.4. DIANA-TarBase

TarBase is one of the most prominent target identifier databases based on high throughput experiments such as microarray and proteomics [54]. TarBase (v1.0), launched in 2006, was the first database for experimentally supported miRNA targets [55]. The latest version (v8.0) contains more than one million entries and more than half a million miRNA-target pairs derived from experiments utilizing more than 33 different low-yield and high-throughput techniques from various species, including *homo sapience, mus musculus,* and *Caenorhabditis elegans*

[54]. Collected data in TarBase are derived from CLIP-Seq/CLASH data sets as well as more than a hundred other high-throughput datasets [56]. Positive/negative interactions can be retrieved by using various filtering options, including species, tissues, cell types, the experimental methodology used, type of validation (direct/indirect), publication details, and the score of *in silico* prediction [54]. miRNA or gene name determines the search strategy in TarBase. The result page comprises gene name, miRNA name, experiments, publications, cell lines, tissues, and prediction score. Then, by clicking on each publication, specific results, such as location, method, result, regulation, validation type, and source will appear. Furthermore, researchers can filter results according to species, method type, regulation and validation type, cell type, tissue, source, publication year, and prediction score [54,56].

4.5. miRNAMap

miRNAMap 2.0 provides an experimentally verified collection of miRNAs and their targets in different species, including insects, vertebrates, and worms. In version (2.0), data from target prediction tools, including Miranda, RNAhybrid, and TargetScan, are combined and used to identify targets of miRNAs in the 3′-UTR region of genes as well as the well-known targets. miRNAMap applies various criteria to reduce the rate of false/positive prediction results and filter the putative miRNA targets. The experimentally validated targets of miRNAs were derived from DIANA-TarBase and the literature. Also, Q-PCR miRNA profiling of 224 human miRNAs in 18 major normal tissues, as well as the expression profiles of miRNAs and their targets are collected in miRNAMap [57].

4.6. TargetScan

TargetScan was launched in 2003 as the first target prediction algorithm for vertebrates' miRNAs [45]. TargetScan is a user-friendly online database which provides the possibility to search by not only miRNAs but also the gene names among several species [27]. Targetscan algorithms predict miRNA targets by searching broadly or poorly conserved sites. The targets are detected by seed matching rules in the 3′-UTR region of protein-coding transcripts [58,59]. For each transcript, the sites targeted by miRNAs are represented based on their different probabilities. Various parameters and algorithms (including site type, context++ score, and PCT) are applied to estimate the probability for each candidate miRNA [1,45,59]. TargetScan ranks through a 'context score,' considering features in the surrounding mRNA, such as local A-U content and location [58]. In TargetScan algorithms, if the search is performed by gene symbol, the results are presented by its various transcripts being categorized as more and less prevalent [27]. On the other hand, if the search is performed by the name of a miRNA, the results are shown on the target genes based on a particular transcript. Thus, through the algorithms and parameters, one can understand the results [1,27,58,59].

4.7. MiRwalk

miRWalk is an open-source platform known as comprehensive databases of validated and predicted MTIs in human, mouse, and rat. miRWalk as a data hub compare the data collected in 13 related databases such as DIANA-microTv4.0, DIANA-microT-CDS, mirBridge, PITA, miRNAmap, miRmap, PicTar2, RNAhybrid2.1, doRiNA, RNA22v2, miRanda-rel2010, miRDB4.0, and Targetscan6.2. Fallowing miRWalk2, a new version was released presenting a new predicting algorithm instead of the data hub feature in the old version [60]. A random-forest-based learning approach, TarPmiR was performed to predict miRNA target sites. miRWalk distinguishes potential miRNA binding sites in the 5′-UTR, CDS, and 3′-UTR [60,61]. This database provides users with options including obtaining data, conducting statistical analyses, and downloading Gene-miRNA networks [60].

4.8. miRGator

miRGator database is defined as a comprehensive source for finding and analyzing functional aspects of miRNAs. This database is applied as a utility for statistical analysis of miRNA targets using databases and annotation categories such as the GO, GenMAPP, and KEGG pathways. The GEO database provides the expression profile of miRNAs. miRGator includes many databases such as PicTar, miRanda, and TargetScan to predict wide genome prediction and target genes. Therefore, since the miRGator algorithm has not conducted de novo predictions, the parameters utilized by this method mirrors the parameters of those three methods. Users can search for miRNAs, target genes, functional types, and miRNA expression profiles. Since this database collects deep sequencing miRNA data, all the data obtained from miRGator is useful for realizing the biogenesis of miRNA and its molecular functions [62].

4.9. miRDB

MiRDB is a user-friendly database developed for miRNA target prediction and functional annotation with a primary focus on mature miRNAs. Due to establishing a wiki editing interface, the users are allowed to make contributions to miRNA functional annotation. Therefore, miRDB is known as a collaborative miRNA database because of providing an interactive community-annotated miRNA functional catalog. miRDB predicts targets of miRNAs in five species, such as humans and mice. To predict targets of miRNAs by training a bioinformatics model with a machine learning method, common features related to miRNA: target binding are integrated. miRDB indicates targets via MirTarget, a bioinformatics tool developed by analyzing interactions between miRNA and their targets derived from high-throughput sequencing experiments. Its new prediction algorithm enables target prediction with user-provided sequences. Predicting targets of cell-specific miRNA is an added feature. Also, miRDB has added a new web query interface to predict miRNA functions by integrative analysis of target prediction and GO data. Researchers can access targets by entering miRNA name, NCBI Gene ID, gene symbol, or GenBank accession number. The classification of the results is based on the target score, which determines the accuracy of the prediction [63–67].

4.10. microRNA.org

MicroRNA.org is a source of target prediction of the miRNAs and expression profiles. Targets of the miRNAs are predicted using the miRanda algorithm, then scored with the mirSVR, a machine learning method for ranking miRNA target sites based on a down-regulation score. The microRNA expression profiles are obtained from a comprehensive sequencing project in more than 250 small RNA libraries derived from human, mouse, rat, tissues and cell lines of normal and disease origin. The improved graphical interface of this database helps users identify the set of genes potentially regulated by a specific microRNA and the implied cooperativity of multiple microRNAs on a particular mRNA target. Also, we can see the graph of the expression levels of the top microRNAs expressed in the tissues and the top tissues in which the specific microRNA is expressed [2,68]. Unfortunately, the last update was in 2010, and this database is out of the limit recently. At the time of writing this review, the latest paper having mentioned microRNA.org was published in 2021. However, because this database has been used in numerous studies, we have described it to ensure completeness.

4.11. DIANA-microT-CDS

The latest version of DIANA-microT, one of the first systems for miRNA target prediction in human, is DIANA-microT-CDS. In this version, an improved algorithm was applied, and the webserver was redesigned completely. DIANA-microT-CDS uses distinct prediction

models to score miRNA binding in both the 3′-UTR and coding sequences (CDs) regions, and then combines them to estimate a single final interaction score. Searching in DIANA-microT-CDS can be performed by miRNA or gene name, Ensembl ID, KEGG description, or a combination of them. In the results, vast information about predicted interactions between miRNA and target genes, and spacious connectivity to online biological resources have been provided. Many features, including providing informative tooltips and online help, make DIANA-microT-CDS one of the easy-to-use tools. Moreover, for advanced users, a Taverna plug-in is presented, providing more options that can be applied to integrate and analyze high throughput experiments data into advanced miRNA analyses [69–71].

The information reviewed so far determines that current target prediction platforms are designed considering different prediction strategies. Hence, it is challenging for researchers to choose the most reliable and appropriate prediction tool to conduct their research [27]. Moreover, besides having strengths, each prediction algorithm has particular limitations. Also, since each tool applies different parameters in their prediction process, over-prediction and diversities in outcomes in large overlapping target lists have often been detected [72]. A tool solely relying on seed matching for target prediction does not consider the evolutionary conservation of the target site's sequence or its accessibility for binding or whether the miRNA:mRNA duplex is thermodynamically stable. Also, since there is evidence on the functionality of many non-conserved binding sites in 3′UTRs [73], using tools filtering by considering only the conservation-based miRNA target prediction can omit miRNA:mRNA interactions in other areas [50]. Being up-to-date is another critical issue since not all tools have regular updating. For instance, TargetScan, DIANA-microT-CDS, and miRDB are regularly updated. Among them, TargetScan covers more species, and miRDB can identify targets in CDSs, 5′UTRs, and 3′UTRs while.

DIANA-microT-CDS can do so in CDSs and 3′UTRs. Moreover, recently the combination of these popular prediction tools is used in several articles [74,75]. Some differential features of these three common prediction tools are summarized in Table 4.

miRTarBase and DIANA-TarBase are two primary databases used for finding validated targets. Both present striking features based on researchers' requirements. miRTarBase covers more spices and provides the opportunity to search based on KEGG pathway and the list of genes or miRNAs of interest, while DIANA-TarBase provides wider options to filter queries, including cell types and regulation type [25,53,54,56]. In Table 5, some features of these two databases are compared. Although they can be used individually, many studies have recently utilized them together [76–78].

Table 4
Differences among three famous target prediction tools.

Tools	Site coverage on mRNA	Input data	Species	Ref.
TargetScan	3′ UTR	Gene symbol, miRNA family	Ten Species, including human	[1,27,45, 59,119]
miRDB	5′ UTR CDS 3′ UTR	miRNA ID, Gene ID, GeneBank accetion, gene Symbol, miRNA sequence, Target sequence	Five Species, including human	[63–65]
DIANA-microT-CDS	CDS 3′ UTR	miRNA ID, Gene ID, kegg descriptions	Four Species, including human	[69–71]

Table 5
Differences among two famous tools for finding validated target.

Tool	Curated miRNA–target interactions	Species	Input data	Ref.
miRTarBase	479,340	32	miRNA ID, miRNA family, Gene symbol, KEGG pathway, validated method, disease name, miRNA list, Gene list	[25, 53]
DIANA-TarBase	~670,000	18	miRNA ID Gene ID gene symbol, Validated method, Validation Type Regulation type Publication Year Cell Type	[54, 56]

5. Databases for finding disease-related miRNA

Dysregulations in miRNAs may result in significant cellular and systematic failures. Previous studies have reported that due to miRNAs' crucial regulatory role, they may participate in the etiology of diseases like cancer, bacterial infections, neurologic disorders, and cardiovascular diseases [79]. Regarding cancer, their contribution may be more complicated as a miRNA may function as a suppressor or an oncomiR [80,81]. In a useful review article, Godlewski et al. have discussed many miRNAs and their target genes which participate in brain physiology and diseases related to neulogic system [82]. Therefore, miRNAs has been introduced as novel promising diagnostic, prognostic and predictive biomarkers [83]. However, there is no coherent knowledge base regarding the relationship between miRNAs and diseases. Therefore, computational tools can help researchers to manage the required data for experiments [84]. In this regard, some operational databases developed to handle miRNAs' involvement in disorders have been mentioned in this review and summarized in Table 2.

5.1. *Mir2disease*

miR2Disease, a manually curated database, presents extensive information on the deregulation of miRNAs in human diseases from literature. Each entry in this database provides information on the relationship between miRNAs and diseases, including miRNA ID, disease name, a summary of the relationship between miRNA and disease, and an expression pattern of miRNAs detected by various methods, including microarray, northern blotting analysis, and qRT-PCR. The experimentally validated target genes collected from TarBase and a literature reference in PubMed are also provided. Also, miR2Disease provides a submission page allowing users to submit novel miRNA–disease relationships. Based on the published article, through reviewing more than 600 published papers, miR2Disease gathered information of 1939 curated relationships among 94 human malignancies and 299 miRNAs. The database is updated bimonthly [85].

5.2. *Human miRNA disease database*

HMDD (Human miRNA Disease Database), known as an early miRNA disease database, is another comprehensive database of miRNA-disease associations. Released in 2018, HMDD v3.0 provides experimentally supported data in human miRNA-disease associations collected from various generalized categories, including genetics, epigenetics, circulating miRNAs and MTIs, and tissue. One of the advantages of HMDD v3.0 is the presentation of two metrics, including disease spectrum width of miRNAs (DSW) and miRNA spectrum width of human diseases

(MSW). The effect of one miRNA in human disorders can be estimated by its DSW scores. Higher scores illustrate broader disease associations of miRNAs. On the other hand, MSW could be employed to assess the complexity of a disease preliminarily. Therefore, high MSW and high DSW can indicate the well-annotated diseases and miRNAs, respectively.

Based on the last updated version on March 2019, 35547 experimentally supported entries, including 1206 miRNA and 893 disorders from 19280 papers, were collected in HMDD v3.2. Moreover, a download link for the data in the HMDD and a submission link for submitting novel data into the database are available [86–89].

5.3. miRcancer

miRcancer is a dedicated miRNA-cancer association database providing a comprehensive collection of microRNA expression profiles in human cancers. It is updated quarterly by text-mining on literature. All the associations are manually validated after automatic extraction from published papers in PubMed. Finding microRNA-cancer associations mentioned in the literature can be performed by searching microRNA and/or cancer names in the searching section. Also, all cancer-related microRNAs are collected in the browsing section. Besides, this website provides two analytical tools (clustering and chi-square analysis) applying analysis on all or a selected pool of miRNA sequences. Based on the last updated version on June 15, 2020, 9080 relationships among 57984 microRNAs and 196 human cancers from 7288 publications are documented in miRCancer. This version uses miRBase (V22) [90,91].

5.4. dbDEMC

Unlike previously introduced databases (miR2cancer, HMDD) which mainly use collection or text mining methods, the database of dbDEMC (differentially expressed miRNAs in human cancers) recognizes the differentially expressed miRNAs in cancer with the analysis of available high-throughput expression data. This database contains 49202 cancer-related miRNAs which associates with 2224 differentially expressed miRNAs. These miRNAs have been extracted from 436 experiments, and are correlated with 36 main cancer types and 73 cancer sub-types. A new update conducted in 2017 contains more types of cancer along with new features to enhance applicability of the database [92]. Most identified miRNAs are related to colon, gastric, and pancratic cancers. dbDEMC contains 1619 more cancer-related miRNAs compared to HMDD and miR2Disease [93].

Among these databases, miRCancer and dbDEMC collect information only from human cancers, while HMDD and Mir2disease provide data from a variety of diseases. HMDD and miRCancer databases have been recently updated [85,86,90,93].

6. Databases for finding SNP in miRNA sequence or target site

By influencing expression levels, processing, and maturation, genetic variations like SNPs can affect the regulatory role of miRNAs. Slight changes in the miRNA binding site in the 3′ UTR can change miRNA: mRNA binding and miRNAs regulatory functions. Therefore, miR-SNPs can have profound downstream effects by altering miRNAs' function and then affecting phenotypes and disease susceptibility [8,94,95]. Studies on SNP-related miRNAs (SNP-miRNA) cover different areas, including the prediction effects of SNPs on miRNAs' targets, the association among SNP-miRNAs and/or expression changes and disease, new SNP-miRNA and isomiRs identification by applying NGS, and development of SNP-miRNA database. According to the essential roles of SNP-miRNAs in complex diseases, several databases and tools have been developed [96], such as those summarized in Table 2.

6.1. miRSNP

MiRSNP is a user-friendly database with a collection of human SNPs in predicted miRNA-mRNA binding sites. This database includes over 414,510 predicted miRNA-related SNPs. MiRSNP provides researchers the opportunity to find putative miRNA-related SNPs from their GWAS and *cis*-acting eQTLs dataset and utilized the results to direct their future functional studies [94].

6.2. MiRdSNP

The miRdSNP serves as a comprehensive repository for disease-associated SNPs (dSNPs) manually curated from the literature published in PubMed. It furnishes robust tools to explore the distance of disease-associated SNPs from miRNA target sites on the 3′-UTR of human genes. This database helps scientists to further investigate the molecular mechanism of gene dysregulation for dSNPs at the post-transcriptional level. In the current version released in January 2012, 786 associations between dSNPs and diseases for 630 unique dSNPs and 204 malignancies are presented [97].

6.3. PolymiRTS

PolymiRTS, an integrated database-cum-Web service, provides information about genetic polymorphisms and their impact on miRNA seed regions and target sites in the human and mouse genomes. Additionally, combined data of miRNA target sites' SNPs, *cis*-acting elements (eQTLs), and the results of GWAS of human disorders is provided in PolymiRTS. Also, to provide more accurate and complete miRNA:mRNA interactions, data of direct mapping experiments like CLASH (cross-linking, ligation, and sequencing of hybrids) are integrated. Also, PolymiRTS provide users the opportunity to explore associations between the PolymiRTSs (Polymorphisms in miRNAs and their target sites) and gene expression traits, biological pathways, phenotypical aspects, and diseases. Besides, users can explore the relevance between the PolymiRTSs and gene expression features, phenotypical aspects, diseases, and biological pathways. Among the tools mentioned above, PolymiRTS is more updated and provides a greater number of features [98].

6.4. IsomiR bank

IsomiR Bank is an online integrative resource containing the sequence and expression information of isomiRs. In this database, 308919 isomiRs data from 4706 mature miRNAs in 2727 samples from eight species are documented. Also, target prediction and the enrichment analysis are presented to estimate the effect of isomiRs on target selection and downstream pathways. Besides collecting isomiRs from NGS data, this database also helps researchers find potential functional isomiRs candidates for further experimental investigations [99].

7. Databases for finding environmental factors

A critical issue in the phenotype of a living organism is the interaction between genetic and environmental factors. Therefore, dysfunctions in miRNAs, environmental factors, and their interactions with the effect on phenotypes can lead to disease. Therefore, developing computational tools for analysis and modeling of miRNA-enviromental factor interactions can shed light on the enviromental factor mechanism, help identify the miRNA signature of enviromental factors, and better understand their interplay role in malignancies. However, although an increasing number of studies have focused on the association between experimental and miRNAs, tools for managing this data and linking miRNAs to experimental factors and phenotypes are still extremely limited [100].

7.1. miREnvironment

miREnvironment database (http://www.cuilab.cn/miren), including a comprehensive set of interactions between miRNAs, environmental factors such as drugs, diet, radiation, and many other factors, and phenotypes, provides researchers with valuable biomedical resource. In this database, the names of miRNAs, phenotypes, environmental factors, conditions of environmental factors, samples, species, evidence, and references were explained. miREnvironment (Last update: Sep-9, 2012) is presented using Django, a Python web framework which integrated more than 3857 entries, 1242 miRNAs, 394 environmental factors, 305 phenotypes, and 24 species from 557 publications. miREnvironment contains pages for browsing, searching (based on miRNAs, environmental factors, phenotypes, and species), submitting new entries to the database, downloading all data in the database, and performing bioinformatics analysis. A list of miRNAs, phenotypes, environmental factors, miRNA Disease Spectrum Width data, and predicted EF-disease (Enviromental factor-disease) association data could be downloaded in text or Excel file. Also, the analysis section provides two main sections: 1. prediction of the result of cancer treatment which aims to predict the outcome of cancer treatment over assessing the enrichment of the miRNA signatures in miRNA oncogenes and miRNA suppressors; and 2. prediction of association between enviromental factor and human disease which seeks to predict the connection between environmental factors and human disease through enrichment analysis of their miRNA signatures based on the HMDD. Ultimately, this section produces the potential disease associated with the given environmental factor [100,101].

8. Databases for finding miRNA in pathways or based on gene ontology

Various studies have demonstrated that miRNAs' targets are significant parts of cellular pathways. In this respect, recent researches have focused on the role of aberrant miRNA expression profiles as biomarkers of pathophysiological conditions leading to disease by modifying genes in significant parts of the molecular signaling pathway(s) [102,103]. Hence, finding the experimentally validated miRNA-pathway associations is essential for future researches. Recently, several bioinformatics resources with a focus on the miRNA-pathway associations have been developed [104]. Some of these databases are presented in this review (Table 2).

8.1. DIANA-mirpath

DIANA-miRPath v3.0, another part of the DIANA framework, is a web-based software designed to links miRNAs to Gene Ontology and KEGG. The database is designed to identify pathways regulated by multiple miRNAs, or the opposite direction, i.e., to discover all the predicted or validated miRNAs significantly targeting a particular KEGG pathway. This database uses predicted data produced by TargetScan or DIANA microT-CDS and/or experimentally validated targets collected in DIANA TarBase, then subsequently combines the interaction results with sophisticated merging and meta-analysis algorithms. This tool conducts advanced analyzing pipelines, including hierarchical clustering of miRNA and pathways, creating heat maps for miRNA-pathway interactions, and detecting pathological SNPs in miRNA binding sites. Generally, DIANA-miRPath v3.0 is a user-friendly web-based tool providing options to manage queries and covering data for seven model species [105–107].

8.2. miRPathDB

miRPathDB (miRNA Pathway Dictionary Database) is a comprehensive resource for miRNAs and their target pathways. miRPathDB enables users to search similar miRNAs, build interactive clustered heatmaps, and determine a set of candidate regulators sufficient to target a gene list of interest. Predicted data are obtained from DIANA-microT, miRDB, and TargetScan. Experimentally validated MTIs are extracted from miRTarBase. It applies an Integer Linear Program (ILP) to automatically extract a set of miRNAs targeting a specific pathway or set of genes of interest. The database contains putative associations among 27452 (candidate) miRNAs, 28352 targets, and 16833 pathways for *Homo sapiens*. In addition to humans, this database contains information about the *M. musculus*, which can be compared to human data and show the degree of conservation between targeted pathways [107–109].

Among these tools, DIANA-miRPath covers more species while miRPathDB only focuses on two. miRPathDB has been recently updated and presents better features. DIANA-miRPath uses signaling pathways from KEGG, whereas miRPathDB utilizes more databases, such as Reactome and WikiPathways. While DIANA-miRPath uses miRBase, miRPathDB utilizes miRBase and miRCarta to provide more information. However, although these tools provide information about the 'miRNA-gene-pathway,' the human 'disease' element is missing [105,107,109,110].

9. Databases and software for finding mRNA-miRNA multiple interactions

Most miRNAs only have modest phenotypical effects, so multiple miRNAs cooperatively regulate their targets. One of the best ways to comprehend complex 'multiple-to-multiple' relations among miRNAs and their targets is using network-based visualization methods. Coupled with proper enrichment analysis support, this strategy will give a profoundly informative presentation to enable essential insights into the miRNAs' underlying regulatory mechanisms [111].

Various databases were developed to accomplish this purpose and help researchers understand miRNAs and their targets through this strategy based on predicted or/and validated miRNA:target interactions. Among these, some of the most utilizable ones are discussed in this review.

9.1. MiRTargetLink

miRTargetLink (https://ccb-web.cs.uni-saarland.de/mirtargetlink/) is a popular tool that provides information about human MTIs in interactive interaction network forms. Also, gene and miRNA set analysis is combined to identify the most relevant biochemical processes affected by the target network. To calculate, depict and visualize interaction networks, miRTargetLink uses data extracted from miRTarBase and miRanda [112]. For downstream analysis, miRTargetLink uses GeneTrail2 and miEAA (a web-based mapping tool and converter among different miRBase versions). Each query can be performed based on entering a different range of miRNAs or genes (from a single one to sets from high-throughput experiments). This software allows users to choose among predicted and experimentally validated targets with strong or weak evidence or their combinations. On the results page, editing and filtering options are provided to help users manage the results [112].

9.2. miRNet

miRNet (https://www.mirnet.ca/) is a user-friendly, visual analytics tool that provides statistical, visual, and network-based approaches to better understand miRNAs' functions. miRNet version 2.0, released in 2020, covers transcription factors (TFs) and SNPs, as well as more information regarding miRNAs, ncRNAs, and disease associations. Here, visual exploration of multipartite networks was improved. Besides, miRNet has developed a flexible interface for data filtering, refinement, and customization during network creation in every query of interest. Moreover, the underlying R package is available to provide more flexible data analysis for advanced users like R programmers [111,113,114].

9.3. MIENTURNET

MIENTURNET (MicroRNA ENrichment TURned NETwork) is an easy-to-use web tool performing a statistical analysis with a fully-featured network-based visualization and analysis. This web tool was created based on the R programming language for statistical computing and graphics. MIENTURNET uses TargetScan and miRTarBase (for predicted and experimentally validated MTIs data). Besides, functional enrichment analysis is performed using annotation databases, including KEGG pathways, Reactome, and Wikipathways. However, the Disease Ontology annotation source is given only for *Homo sapiens*. MIENTURNET accepts a list of mature miRNAs or mRNAs as input and inferring possible evidence (computational or experimental) of the regulatory effect of miRNAs on target genes based on statistical analysis for over-representation of interactions among miRNAs and their targets. Therefore, using MIENTURNET, researchers have an opportunity to consistently perform both statistical and network-based analyses using a single tool and receive a more effective prioritization of the interaction among miRNAs and their target genes [115].

Among all these excellent tools developed for miRNA network analysis, miRNet 2.0 supports 11 Species, while miRTargetLink and MIENTURNET cover 1 and 6 species, respectively. Unlike the others, miRNet 2.0 covers libraries on TFs, SNPs, ncRNAs, disease associations, Expression profiling, and PPIs (protein-protein interactions). Also, miRNet 2.0 has the most comprehensive network visual analytics by providing multiple query types and multipartite network visualization [112,113,115].

10. Conclusion and prospects

Despite a large body of research on miRNAs, our understanding of these molecules and their regulatory mechanisms is still limited. Besides, the studies have generated diffused data. To this end, bioinformatics tools have been developed to manage this dispersed data [27]. These tools are categorized according to the information they provide for users to understand all aspects of miRNA research. In this article, functional databases were reviewed under categories used in various miRNA-related studies. Tools are chosen based on the researcher's needs and purposes. For example, when researchers focus on miRNAs involvement in the regulation of a specific gene, TargetScan has a significant advantage because of the provision of isoforms, while DIANA-microT does not distinguish between them [27,59,69]. However, each database has its advantages and disadvantages that must be taken into account when deciding to use each tool. A major limitation is creating large amounts of false outputs, including false negatives resulting from mistaken deletion of candidate lists or false positives due to increased sensitivity [28,29]. For example, TargetScan, as the most accurate sequence-based tool, has a high false negative rate leading to low sensitivity [27,59,69]. Instead, the DIANA-microT tries to be balanced, therefore apply a parameter to compare its results to those from other tools [27,59,69]. Using programs based on Machine-learning (ML) and filter-based algorithms reduces the number of false positive/negative results and provides higher sensitivity [116,117]. Due to various algorithms and different versions of primary repositories that each database uses, there may also be discrepancies between the results of a similar query in different databases (for example, different versions of miRBase have been applied) [31,46]. This diversity can make changes in the number and types of miRNAs or target genes, in the nomenclature, and the other outcomes. For example, miRDB and miRTarBase, in their last update, use the last version of miRBase (V22) [26,53,65]. miRanda is a reference database used in miRTargetLink. Of note, the last version of miRanda was updated in 2010. In contrast, MIENTURNET uses two of the most updated databases, TargetScan, and miRTarBase to accomplish its purposes [112,114,115]. Converter tools can also be useful to solve the problem of using different versions of MiRBase [46]. Although it is best to use several tools simultaneously to solve the problem of diversity in the results of various tools, this method is not suitable if the final results require ranking. A single, suitable tool should be utilized in such studies according to experimental design [31]. In addition, it is advisable to use integrated systems and hubs that include several computational tools and algorithms, which may have better outputs than a single one [60,118]. Regular updating and facility of download and upload of information to online databases are the other useful features for improving these tools. As an example, HMDD presents a download and a submission link for adding novel data into the database [86], and miRTarBase is updated more than other similar databases [53]. Given that all computational algorithms ultimately require experimental validation, the best results are likely to be obtained by a comprehensive review of a combination of tools with multiple approaches [111,112,114]. Although high-throughput technologies have greatly enhanced our knowledge of miRNAs, the analysis and management of their information require more analytical, sophisticated, and user-friendly tools [54]. Thus, designing regularly updated comprehensive tools that cover different aspects of miRNA studies and provide more accurate features for users to search with, can be very helpful for future studies of researchers [115].

Declaration of competing interest

All authors indicate there is no conflict of interest.

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